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By Aviel Goodman

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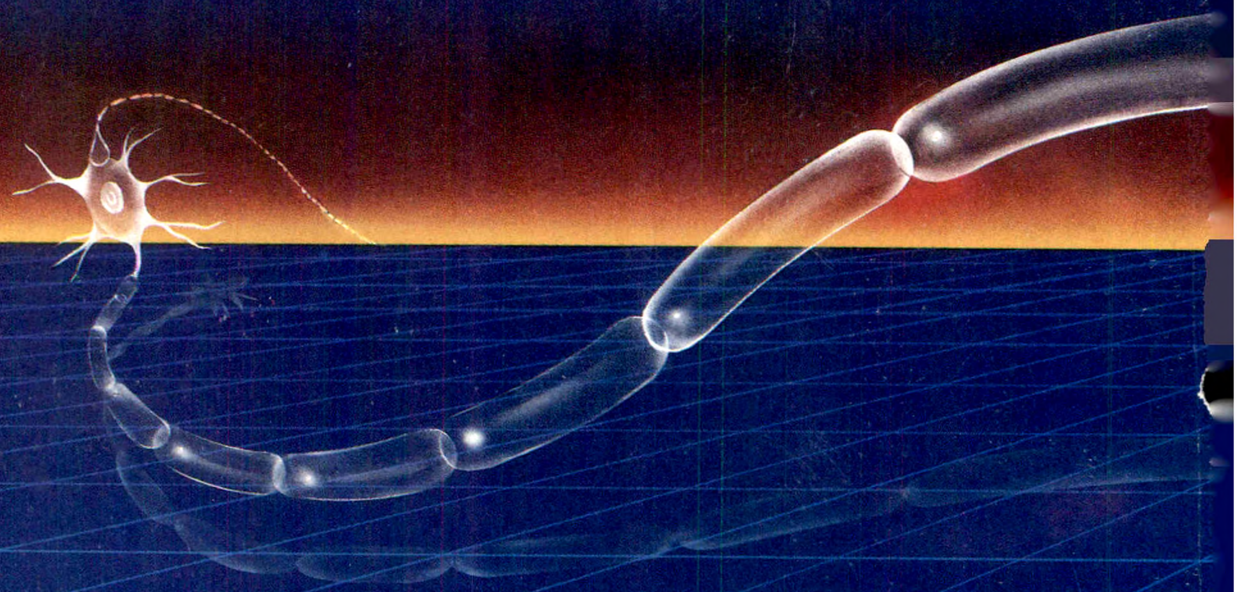

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THE AMERICAN JOURNAL OF PSYCHIATRY
*Special Articles*

# Organic Unity Theory: The Mind-Body Problem Revisited

Aviel Goodman, M.D.

*The purpose of this essay is to delineate the conceptual framework for psychiatry as an integrated and integrative science that unites the mental and the physical. Four basic philosophical perspectives concerning the relationship between mind and body are introduced. The biopsychosocial model, at this time the preeminent model in medical science that addresses this relationship, is examined and found to be flawed. Mental-physical identity theory is presented as the most valid philosophical approach to understanding the relationship between mind and body. Organic unity theory is then proposed as a synthesis of the biopsychosocial model and mental-physical identity theory in which the difficulties of the biopsychosocial model are resolved. Finally, some implications of organic unity theory for psychiatry are considered. 1) The conventional dichotomy between physical (organic) and mental (functional) is linguistic/conceptual rather than inherent in nature, and all events and processes involved in the etiology, pathogenesis, symptomatic manifestation, and treatment of psychiatric disorders are simultaneously biological and psychological. 2) Neuroscience requires new conceptual models to comprehend the integrated and emergent physiological processes to which psychological phenomena correspond. 3) Introspective awareness provides data that are valid for scientific inquiry and is the most direct method of knowing psychophysical events. 4) Energy currently being expended in disputes between biological and psychological psychiatry would be more productively invested in attempting to formulate the conditions under which each approach is maximally effective.*

(Am J Psychiatry 1991; 148:553–563)

The field of psychiatry represents the intersection and potential synthesis of perspectives offered by physiology, psychology, and philosophy. Within the domain of psychiatry, issues from these areas may be explored in terms of their implications for clinical practice, research, theory, and metatheory. One particular issue epitomizes the intersection of physiology, psychology, and philosophy, with major implications for all of psychiatry from metatheory to clinical practice: the relationship between mind and body, between the mental and the physical. One of the oldest and most widely addressed issues in the history of thought, it has recently assumed a heightened practical significance in the context of current efforts to define the nature of psychiatric illness and the proper role of psychiatric treatment.

A review of the literature on this subject (1) revealed four fundamental theories concerning the relationship between mind and body, or the mental and the physical, each articulated by a prominent seventeenth-century philosopher.

Leibnitz espoused psychophysical parallelism, according to which mind and body are ultimately different forms of reality existing in a preestablished harmony with no influence on each other. This theory is implausible because it denies the influence of mental

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processes on behavior as well as on physiology and ignores the evidence for the influence of physiology on mental processes.

Psychophysical dualism, championed by Descartes, shared with parallelism the dualistic thesis that mind and body are different forms of existence but added that they interact with and influence each other.

Hobbes advocated the theory of materialism: reality is a physical reality, and a different, nonphysical reality consisting of mental phenomena does not exist. This theory has evolved three basic ways of understanding mental phenomena. 1) The mental is reducible to the physical and may be completely explained by analysis of underlying physical processes (reductionism). 2) Mental phenomena are epiphenomena, secondary "accidental" effects of physical processes. 3) Mental phenomena are emergent relative to physical phenomena—they are systemic wholes arising from the interaction of physical processes and have systemic properties not reducible to the properties of their constituents (this is related to general systems theory).

The fourth fundamental theory, mind-body identity, was articulated by Spinoza. He maintained that brain processes and mental states are one and the same thing or different ways of comprehending the same thing.

## THE BIOPSYCHOSOCIAL MODEL

The biopsychosocial model is at this time the preeminent theoretical framework in medical science that addresses the relationship between mind and body. It evolved from studies in general systems theory and its application to biology, particularly the work of von Bertalanffy and Weiss. The formulation and exposition of the biopsychosocial model as a medical theory have been primarily the work of George L. Engel, with notable contributions concerning behavioral medicine from Gary E. Schwartz. Less than 20 years old, the biopsychosocial model is now the most coherent, comprehensive, and empirically valuable conceptual framework within which to understand the human being in health and in illness.

The basic thesis, noted by Weiss and recapitulated by Engel (2), is that nature is ordered as a hierarchically arranged continuum with the more complex, larger units superordinate to the less complex, smaller units. Each level in the hierarchy represents an organized dynamic whole, or system, and each system implies qualities and relationships distinctive of that level of organization. Meanwhile, nothing exists in isolation, and every system is influenced by the configuration of systems of which it is a part. All levels of organization are linked, so that change in one effects change in the others.

From another perspective, an event does not occur on any particular level but may be approached, perceived, investigated, and understood on any of several levels. An event can be conceptualized as interpersonal, psychological, physiological, or even biochemical, depending on the level of analysis involved. According to this theoretical schema, as emphasized by Schwartz (3), the "split" between mind and body does not inhere in the nature of reality but, rather, in the difference between levels.

Engel (2) noted that each system requires criteria for study and explanation which are unique to that level. Consistent with this idea, but having further implications, is Dismukes's comment (4) that at each level there appear properties unique to that level which can be described to some degree in terms of lower-level functions, but never completely. This introduces the concept of emergence, a central principle of general systems theory and the feature of the biopsychosocial model that directly addresses the relationship between mind and body. Emergence, as described by Schwartz (3, 5), signifies that the properties and functioning of a system as a whole emerge out of the dynamic interaction of the components that make up the system. Bunge (6) noted that emergent properties are those which characterize a system as a whole and which no system component has, and Allen et al. (7) stated that emergent properties cannot be predicted or deduced from the properties of component elements. These points have been used in arguments to refute reductionism.

In applying the concept of emergence to the mind-body issue, Bunge (6) proposed that the mental be conceived of as emergent relative to the physiological. Roger Sperry (8) has been one of the foremost proponents of conceptualizing mental phenomena as "dynamic emergent properties" of cerebral excitation, inseparably tied to but "different from and more than" material brain processes (p. 533). In another paper (9), Sperry wrote, "Once generated from neural events, the higher order mental patterns and programs have their own subjective qualities and progress, operate and interact by their own causal laws and principles which are different from and cannot be reduced to neurophysiology (p. 201). To emphasize that he was not proposing a form of dualism, Sperry (9) added to emergence the concept of embodiment. According to this principle, mind is not a form or state of existence different from brain but an organizational or functional property of brain processing. It is constituted of physiological and physicochemical activity embodied in and inseparable from the active brain. MacKay (10), when discussing the embodiment of mind in brain, suggested that mental processes are embodied in brain processes as the solving of an equation is embodied in the workings of a computer.

The biopsychosocial model is thus a systems theory according to which nature is ordered as a hierarchy of systems; the person (experience and behavior) is identified as a whole composed of and superordinate to the nervous system (and other organ systems). Focusing on the relationship between mind and body, this theory conceptualizes mental phenomena as emergent relative to the nervous system; they are constituted of and generated from physiological and physicochemical events but are characterized by emergent properties different from and irreducible to neurophysiology. This is an elegant and satisfying model, integrating diverse realms of science in one schema that accords mental phenomena full epistemological status while apparently steering a clear course between the Scylla of reductionistic materialism and the Charybdis of dualism. Closer scrutiny, however, indicates the course to be less clear on the sea than it is on the chart.

In a hierarchy of systems, relationships exist between the interactions of states, events, and properties on one level and the emergent states, events, and properties on the next higher level, whether these are designated as causal relationships, rules of composition, or transformation laws. If one system is to be characterized as emergent relative to another, a description of these relationships—albeit incomplete—must be available or there is no basis for the characterization. As postulate 2 of Bunge's exposition of emergence states, "Every emergent property of a system can be explained in terms of properties of its components and of couplings among them (6, p. 503). It follows, then, that for each ordered pair of systems, one emergent relative to the other, there exists a coherent language in which to formulate, describe, and explain these relationships. And this language must be logically and semantically continuous with the languages of description/explanation associated with each of the systems, the relationship between which is the subject under consideration. Such descriptions are not available for the relationship between mental states, events, and properties and neurophysiological states, events, and properties. This in itself is not necessarily a problem for the theory that the mental is emergent from the physical, since it could be argued that the formula of translation has simply not yet been discovered or formalized. More problematic, though, is the lack of a coherent linguistic bridge. There is no system of terms that is logically and semantically continuous with both mental terms and neurophysiological terms.

Emergence theories, however, may not be threatened by the lack of a linguistic bridge. Sperry, a major advocate of emergence, wrote that mental qualities are "of a very different quality from the neural, molecular, and other material components of which they are built" (9, p. 204). It may be that this qualitative difference is sufficient to preclude a coherent language that can connect with each system's semantic/logical network and provide a description of the relationship between them. Although Sperry insisted that his theory did not constitute dualism, it appears that he had become caught in a bind in which he was unable to deny reductionistic materialism without affirming something that looks very much like dualism. Popper and Eccles (11), while also maintaining that mental processes are emergent relative to physical processes, clearly identified their theory as psychophysical dualism with interaction. They stated that while brain activity is a necessary condition for mental processes, mental processes are epistemologically distinct from brain processes. They proposed that the relationship of the brain to the self is that of computer to programmer, with the self-conscious mind exercising a superior interpretative role with respect to neural events.

While acceptance of dualism may preserve the integrity of the biopsychosocial/emergent model, it reintroduces serious weaknesses, the obviation of which was among the model's major attractions. Bunge, a proponent of emergence theory, dismissed psychoneural dualism as "barren double talk and . . a disguise for ignorance" (6, p. 505). He objected to the theory on the logical grounds that it is not falsifiable by empirical data. While falsifiability is not necessarily the touchstone of scientific validity, lack of falsifiability tends to undermine a theory's credibility. Meanwhile, MacKay (10) stated that the additional entities postulated by dualism are not required by the available evidence—an argument against dualism based on Ockham's razor, or the principle of parsimony. Bunge (6) further complained that dualism has failed to define "mental substance," which is necessary because 1) there must be a mental substance in order for there to be mental states—in Bunge's words, "A state must be a state of something" (p. 502)—and 2) the definition must denote a logical and epistemological difference from physical substance (and physical phenomena) in order to maintain the claim of dualism. Perhaps the most decisive argument is that dualism fails to account adequately for the causal relationship between mind and brain, as first argued by Kant: how could a mind with no spatial existence or extension influence a physical brain extended in space? More recently, Fodor (12) wondered how a nonphysical mind can give rise to physical changes without violating the laws of conservation of mass, energy, and momentum. Furthermore, if a mental force that could influence physical entities and processes were postulated, it would then by definition also be a physical force, which would not be consistent with dualism.

General systems theory, with its attendant concept of emergence, is applicable to much of science, and its expression in the biopsychosocial model appears to be a natural and intuitively pleasing extension of the theory. Yet the emergence relationship between mind and body seems to require some form of psychophysical dualism, which is in turn untenable.

## MENTAL-PHYSICAL IDENTITY THEORY

It may be recalled that the mental-physical, or mind-body, identity theory, as formulated some 300 years ago by Spinoza, proposed that brain processes and mental processes are the same thing or different ways of conceptualizing the same thing. The following version may provide more clarity and precision. A certain class of events is referred to by two different classes of terms, mental terms and physical terms. The event (or state or process) referred to by any given mental term is identical to the event (or state or process) referred to by some physical term. Each class of terms (or language or conceptual network) is associated with its own way of knowing or experiencing. The phenomena themselves are inherently neither mental nor physical; it is the ways of describing, conceptualizing, and experiencing them that belong to one or the other of the categories represented by these terms.

It is instructive to consider how the classes of mental and physical terms can be defined or, more specifically, distinguished. As Feigl (13) demonstrated, the physical is ultimately defined as "the sort of objects and processes which can be described in the concepts of a language with an intersubjective observation basis" (p. 54). Physical terms are associated with statements that are intersubjectively confirmable, whereas mental terms are associated with statements that are only subjectively confirmable. Thus, mental and physical are to be understood not as kinds or aspects of reality but, rather, as languages or conceptual systems associated with different forms of knowledge or ways of knowing/experiencing.

This difference has been described in various ways. The psychoanalyst Sandor Rado characterized conscious experience as the "inward self-expression" of neurophysiological activity (14), the former known by introspection and the latter known by inspection (15). Feigl (13) distinguished between knowledge by acquaintance (direct experience), which conveys "intrinsic nature," and knowledge by description or indirect manifestation. He noted that in most of science, we know only the description or indirect manifestation and posit the intrinsic nature. It is only in the case of psychoneural events that both forms of knowledge are available. Maxwell (16) similarly identified conscious experience with knowledge of intrinsic properties but contrasted that knowledge with the knowledge of "causal roles, structural properties, and positions in causal-structural networks" provided by physical science. Physical science asserts the existence of instances of a variety of intrinsic properties and imparts information about their various causal and structural relationships; however, it provides no knowledge of these intrinsic properties themselves. Globus noted that the distinction between what the subject experiences as consciousness and what the observer experiences as neural events is essentially a difference in access to information. He wrote, "Concerning what is going on in my 'neuropsyche,' I have direct or first order access which I experience as consciousness; and an observer looking into my neuropsyche has indirect or second order access which he/she experiences as representations in his/her consciousness of neural events" (17, p. 156).

The idea of identity also merits further exploration. Identity of two concepts connotes identical meaning. There are three dimensions to the meaning of a concept: its referent, its place in and relationship to other concepts in a conceptual network, and its confirmatory evidence (actual and/or possible data that constitute its evidential base). Each dimension of meaning is a dimension of potential identity. Extensional identity denotes a shared referent. Intensional identity between two concepts obtains when they are substitutable for each other because they have the same relationships to other concepts in a conceptual network. Empirical identity describes a condition in which the confirmatory evidence for both concepts is the same. The theory of mental-physical identity pertains first of all to identity of reference or extension: mental terms and corresponding physical terms have identical referents, or designata. Intensional identity of mental concepts with physical concepts is logically ruled out by the definitions of mental and physical as signifying and constituting separate conceptual networks. Some degree of identity (metaintensional?) between the logical or formal characteristics of mental language and those of physical language is hypothesized, however; that is, the formal structures of the relationships among some mental concepts are identical to the formal structures of the relationships among some physical concepts.

Another version of this hypothesis states that there exist isomorphisms between certain configurational (gestalt) features of the mental conceptual network and certain configurational features of the physical conceptual network. Empirical identity is doubly precluded. On the one hand, the relationship between a concept and its evidential base entails also its relationship to concepts referring to actual or possible confirmatory data, so both the concept in question and its confirmatory data must be in the same conceptual network. Mental concepts would thus be confirmed by mental data and physical concepts by physical data. (Isomorphism of the relationship of concept to confirmatory evidence is possible, but not identity of confirmatory evidence.) On the other hand, as just discussed, mental and physical concepts are associated with different ways of knowing. Hence, the processes of confirmation, beginning with the criteria for validity of data, would be different for each set of concepts.

The central postulate of the mental-physical identity theory is that for every mental concept there exists a physical concept with the same referent. The mind-body problem thus becomes, as Carnap (18) noted, not an ontological or scientific problem but one of logical analysis—a matter of the relationship between mental concepts concerning the data of first-person phenomenal experience and physical concepts concerning behavior and neurophysiology. The first question is, Can such a relationship be delineated? Are mental terms and statements translatable into physical terms and statements?

Graham (19), in explicating his thesis of linguistic parallelism, claimed that statements in one language could be translated into the other. Others, notably MacKay and Feigl, have argued against translatability on the grounds that the mental and the physical represent not only different languages but also different logical or categorial types. MacKay (20) maintained that statements about conscious experience and statements about correlated brain activities are "logically complementary" and that statements of either type are logically irreducible to statements of the other. In another paper (21), MacKay differentiated this complementarity from the well-known complementarity of the wave and particle aspects of light, noting that the mental and the physical "are not symmetrically related but belong to different conceptual levels which are not intertranslatable" (p. 1390). As already noted, identity theory states that for every mental concept there exists a physical concept with the same referent. The converse statement—that for every physical concept there exists a mental concept with the same referent—is not a component of identity theory. Feigl (13) agreed with MacKay to the extent of denying purely analytical (logical) translatability between statements in the two languages, but he carried the discussion a step further. He distinguished analytic translation from cross-categorial correspondence rules connecting phenomenal and physical terms, statements that specify which physical term corresponds with a phenomenal term (i.e., has the same referent). In another paper (22), Feigl referred to these rules as "empirical identifications,"—statements functioning as hypotheses about correspondence between phenomenal concepts and physical concepts, the substantiation of which requires empirical evidence. Feigl did not, however, specify what form this evidence should take. He noted that the correspondence rules should be formulated in a "semiotic (semantic-pragmatic) metalanguage" (13), which would seem to be most appropriate also for the conceptualization of confirmatory evidence. Again, though, it is not clear how such a cross-categorial language would be constituted.

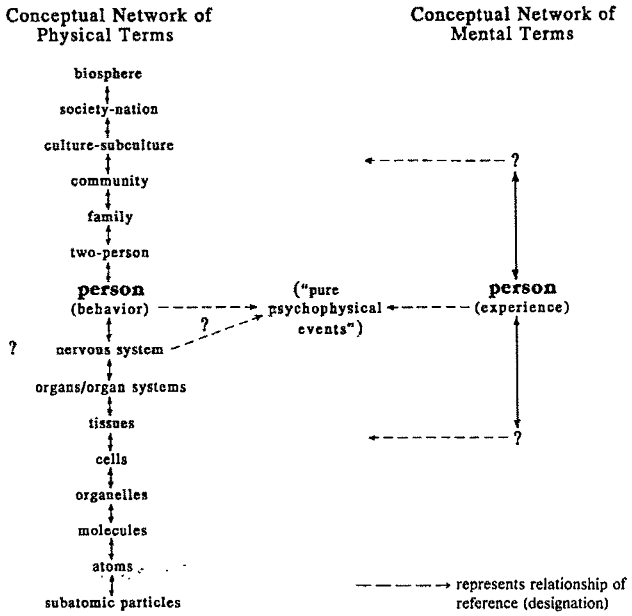
The issue of translatability, particularly as formulated by Feigl, highlights the important distinction between the mental-physical identity theory and hypotheses about mental-physical correspondence. The identity theory postulates that the referent of a mental term is identical to the referent of a corresponding physical term. It describes a general relationship between the mental and physical conceptual networks. Hypotheses of correspondence, meanwhile, concern the relationship of coreference between specific mental and physical concepts or classes of concepts. They are provisional statements, the validation of which depends on empirical evidence. Many proponents of mental-physical identity theory have formulated it as identity of reference between mental (psychological, phenomenal) and neurophysiological terms. This, however, is not the identity theory but a hypothesis of correspondence between mental concepts and the class of concepts in the physical conceptual network that are at the neurophysiological level of organization. The discovery of a mental concept for which there is no corresponding neurophysiological concept (i.e., no neurophysiological concept with the same referent) would refute this particular hypothesis but not the mental-physical identity theory. The identity theory does not exclude the possibility that physical concepts which correspond to mental concepts may belong to some level of organization in the network of physical concepts other than the one represented by neurophysiology.

To bring together the threads of the preceding discussion, the mental-physical identity theory may be presented as follows. There exist "pure psychophysical events" that the subject and the observer experience differently, that they derive different knowledge from, and that they designate with different classes of concepts. The subject experiences these events as conscious phenomenal awareness—which yields direct knowledge, by acquaintance (first-order access), of the intrinsic nature of the events—and designates them by mental concepts that are confirmable only subjectively. The observer experiences these events as behavioral and/or physiological data—which provide knowledge, by description, of the causal/structural relationships of these events (as well as second-order access to the subject's experience)—and designates them by physical concepts that are intersubjectively confirmable. The identity between mental and physical concepts has two components: extensional identity of the events to which the concepts refer (the pure psychophysical events) and some degree of metaintensional identity deriving from the isomorphism of structures and relationships within each conceptual network.

Feigl (23) emphasized that the mental and the physical are not two realms or concomitant types of events but one reality represented in two conceptual systems. Globus, meanwhile, rejected the claim of a single reality: "There is no single reality, as reality cannot be conceived of independent of the perspective by means of which 'reality' is assessed" (17, p. 169). Globus's argument appears to represent the position of epistemological idealism, perhaps informed by developments in modern physics. Feigl, whose position resembles epistemological realism, seemed less concerned with the idealism-realism controversy than with exploring the semiotics. In any case, there is no significant incongruity in how these perspectives affect mental-physical identity theory. Similarly, a question may be raised concerning the "pure psychophysical events": do they really exist? Presumably, Feigl would answer yes, while Globus would answer no. In pragmatic terms, the answer is that it does not matter. Whether they are postulated as an underlying reality or dismissed as convenient fiction, they would not be demonstrable, and the distinction would have no practical significance.

The foregoing examination of the mind-body problem, while not providing a solution, circumscribes it to the realm of logical analysis and suggests some guidelines according to which it may be more successfully approached. In this context, it may seem perplexing that mind-body issues have been considered so problematic. What emerges is another sense in which the mind-body problem is a problem of logical analysis. Most of the enigmas and conundrums related to the mind-body problem in philosophy and science originate from the mixing of terms from conceptual systems of different logical or categorial types. Confusion

**FIGURE 1. The Realm of Science [Systems Hierarchies]: Engel's Diagram Modified According to Mental-Physical Identity Theory**



arises and mistakes emerge when one attempts to make causal links between events or processes described in terms from one conceptual network with events or processes described in terms from another conceptual network of different logical/categorial type. This condition permeates the fabric of ordinary language, which reflects a dualist/interactionist view of the relationship between the mental and the physical. These biases and limitations in turn affect scientific literature, even when its intent is explicitly antidualistic. Graham (19) documented numerous instances of mind-body dualism or interactionism in medical literature. Even the word "psychosomatic" is generally used in such a way as to imply that mind and body exist separately but are connected by some sort of interaction. Since the language we learn (content and process) defines the concepts and establishes the conceptual relations according to which we perceive, organize, and understand our experience, it is evident that logic and epistemology are not clearly separable from semiotics (study of language processes, including semantics, syntactics, and pragmatics). It is also evident that the transcendence of dualistic thinking entails more than the decision to adopt a new theory.

## ORGANIC UNITY THEORY

Although the biopsychosocial model is the most comprehensive and useful model in medicine that addresses the relationship between mind and body, there are serious flaws in the view of mind or mental phenomena as emergent relative to physiological processes. The mental-physical identity theory constitutes the most coherent and logically sound philosophical understanding of the relationship between mind and body but provides no tangible link with the conceptual network of medical science. The organic unity theory proposed here is a synthesis of the biopsychosocial model and the mental-physical identity theory, an integration of medical science and philosophy.

Engel represented the biopsychosocial model in an elegant diagram that illustrated in vertical array the hierarchy of natural systems, ranging from subatomic particles to the biosphere (2, p. 537). At the middle level of the diagram, above or superordinate to the physiological level (labeled "nervous system" by Engel) and below or subordinate to the interpersonal level (labeled "two-person" by Engel), is the level of the single, whole person, which Engel labeled "person (experience & behavior)." It is in this characterization of person as experience and behavior that the flaw of the biopsychosocial model is exemplified. Experience is a mental concept, representing direct, first-order knowledge by acquaintance that is confirmable only subjectively; behavior is a physical concept, representing knowledge by description that is intersubjectively confirmable. As discussed in the preceding section, experience and behavior belong to distinct conceptual networks, which are of different logical or categorial types. Similarly, as noted earlier, there are problems with the statement that phenomenal experience is emergent relative to physiological processes. It is significant that the names of all the other levels or systems in the diagram subsume sets of concepts that represent knowledge by description, which is intersubjectively confirmable. In other words, the entire diagram, with the exception of experience, is constituted of physical concepts. If the diagram is to be logically consistent, experience must be removed from what seems to represent the conceptual network of physical terms and be placed in another diagram that represents the conceptual network of mental terms.

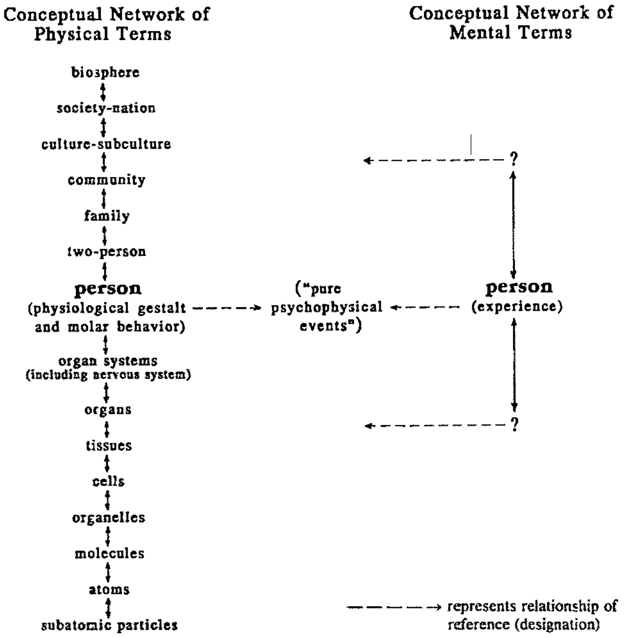
This change has been made in figure 1, a diagram similar to Engel's but which incorporates the modifications indicated by mental-physical identity theory. In this provisional schema the biopsychosocial model, with its hierarchy, emergence, and other features of general systems theory, is preserved intact. The realm of science is represented and known as two linguistic/conceptual networks: the mental and the physical. On the physical side are terms which designate systems of events, states, and processes that are known by description and are intersubjectively confirmable. On the mental side are terms which designate systems of events, states, and processes that are known directly by acquaintance and are confirmable only subjectively. In between, in parentheses, are terms which represent systems of events, states, and processes (either postulated or imaginary, but in any case indemonstrable) to which both mental and physical concepts refer.

As indicated by the question marks in figure 1, several issues remain unresolved. The conspicuous asymmetry of the diagram, with several systems specified on the physical side and only one on the mental side, suggests the possibility that there may be other levels of organization which could be designated by mental terms. Such a notion has received support from academic as well as spiritually oriented sources. Wittgenstein (24) maintained that the private process of experience is embodied in the public world of the subject's behavior in his or her particular social context, not only in his or her brain. This idea was echoed by Booth, who explicitly extended mind-brain identity to mind–physical-world identity. He wrote, "Mental processes form causal chains at a level of analysis in terms of meaning which is complementary to analysis at the physical level; physical causation runs through a system in which brain and environment are integrated" (25, p. 348). Approaching the issue from an information-processing orientation, MacKay (21) wrote, "Relevant flow-lines [of information] would in general extend beyond the confines of any one component structure, and during conscious action might even run out-and-back through the environment" (p. 1389). The anthropologist Gregory Bateson (26) was developing a similar idea when he wrote, "The mental world—the mind—the world of information processing—is not limited by the skin." Conceptualization of this possibility—of levels of organization of mental systems other than the human nervous system—is limited by the difficulty in attributing phenomenal experience to levels of organization designated by subpersonal or suprapersonal terms and in imagining what other forms of mental properties there might be at these levels.

The question mark at the left of figure 1 refers to the ordering of the physical systems hierarchy as it is portrayed in the diagram, which reflects Engel's portrayal in the original diagram (2). It is clear that the nervous system is not composed of, emergent from, or superordinate to other organ systems. It, like the others, is emergent from and superordinate to the organs and tissues from which it is composed. And there is a physiological system (not mentioned in Engel's original diagram) that is composed of, emergent from, and superordinate to the organ systems, including the nervous system: the whole physiological gestalt of the human organism. This system would be at the same level of hierarchical organization as the intersubjectively confirmable molar behavior (behavior as a whole) of the organism described as a person by an observer; and both would seem to be at the same level as the direct awareness of the organism experienced as "person" by the subject himself or herself.

This leads to the question indicated by the other question mark, left of center in figure 1: at which level of organization in the physical conceptual network are the terms that correspond to (i.e., have the same referent as) phenomenal/experiential terms? This is an issue not of logical analysis but of empirical identification, as discussed in the preceding section. Statements of mental-physical correspondence are hypotheses, the substantiation of which requires empirical evidence. It is hypothesized here that the physical terms that correspond to phenomenal/experiential terms may be found at the organismic level of organization, represented by the emergent physiological gestalt on the one hand and molar behavior on the other.

**FIGURE 2. The Realm of Science (Systems Hierarchies): Engel's Diagram Further Modified According to Organic Unity Theory**


Conceptual Network of Physical Terms
Conceptual Network of Mental Terms
biosphere
society-nation
culture-subculture
community
family
two-person
person
(physiological gestalt and molar behavior)
("pure psychophysical events")
person
(experience)
?
organ systems (including nervous system)
organs
?
tissues
cells
organelles
molecules
atoms
subatomic particles
represents relationship of reference (designation)

The additional modifications of the diagram suggested by the preceding discussion are incorporated in figure 2.

## IMPLICATIONS FOR PSYCHIATRY

Organic unity theory entails a range of implications for psychiatry, from theory to research to clinical practice. Some of these will now be considered.

### *Theory*

Among the implications of organic unity theory for psychiatry, perhaps the most salient is the dissolution of the apparent dichotomy between the biological (organic) and the psychological (functional). It has been mentioned that inherent in current language, and in the conceptual structures which it defines in infancy and later expresses, is a dualist/interactionist view of the relationship between the mental and the physical. Consistent with this linguistic/conceptual framework, psychiatric disorders have been regarded as a result of the summation or interaction of biological and psychological factors and have been classified according to these factors' relative preponderance. Listed at the more biological end of the spectrum are bipolar disorder (manic-depressive illness), schizophrenia, and major depression. Genetic studies have demonstrated

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hereditary transmission of these disorders, effective pharmacotherapeutic agents have been developed and are in widespread use, and coherent biological theories have been formulated to explain both pathogenesis and the actions of psychotropic medications. At the psychological end of the spectrum are placed neurotic conditions and personality disorders, which are more responsive to psychological therapies and less responsive to psychotropic medications.

According to organic unity theory, the distinction between the biological and the psychological pertains to the separate conceptual networks, not to the referents of these concepts. Each event or process involved in the etiology, pathogenesis, symptomatic manifestation, and treatment of psychiatric disorders is not either biological or psychological; it is both biological and psychological. Certainly, each conceptual system has varying degrees of adequacy in characterizing (furnishing terms to describe) and explaining (relating these terms to others in the causal/structural network) different psychiatric syndromes or disorders. This, however, reflects not the inherent nature of the disorders but, rather, the limitations of the conceptual systems. Neurotic conditions and personality disorders are no less biological than are schizophrenia and mood disorders, and the latter are no less psychological than the former. Perhaps schizophrenia and mood disorders are considered to be more biological because they have more known features that readily fit the schemata for biological data and they have been more clearly defined in intersubjectively confirmable terms. In addition, available pharmacological agents more specifically and reliably alter their more clearly defined symptoms. The argument that genetic evidence for hereditary transmission indicates a biological rather than a psychological disorder is predicated on the erroneous equation of genetic with biological and of psychological with environmental, as well as on the erroneous dichotomization of the biological and the psychological. What is inherited are genetically encoded predispositions to the development of events and processes (or patterns thereof), which may be referred to by and understood in terms of both biological and psychological concepts. This is as true for neurotic conditions and personality disorders as it is for schizophrenia and mood disorders.

Conceptualization of this principle may be facilitated by considering theories about genetic/hereditary contributions to language acquisition (syntactic structures) and the potential for cognitive development, both of which are processes generally formulated in psychological terms. While research concerning specific hereditary factors in neurotic and personality disorders is by no means complete, it is likely that these disorders involve predispositions to the development of 1) temperament variables, including activity level, rhythmicity or regularity, approach versus avoidance tendencies, adaptability, threshold of responsiveness, quality of mood, intensity of mood response, and attention ability (27, 28), 2) style of cognitive functioning (e.g., global and diffuse versus focused and detailed), 3) introversion (inner-orientedness) versus extraversion (other-orientedness), and 4) precursors of ego functions, including affect tolerance, affect regulation, impulse control, reality testing, and synthetic/integrative ability. Often, it is assumed that psychodynamic concepts refer to processes that have no biological basis. A more accurate statement is that what is lacking is not the biological basis but, rather, the linguistic/conceptual schemata (as well as neurophysiological knowledge) with which to describe and understand the biological aspects of the processes to which psychodynamic terms refer.

### *Research*

In neuroscience research there has been a reductionistic tendency to search for causes or correlates of psychological phenomena in specific areas of the brain or in the activity of certain neurotransmitters (or their receptors). The data thus gathered and the theories constructed have proven to be fascinating and useful but of limited value in furthering understanding of conscious experience. Organic unity theory indicates that conscious experience is more likely to correlate with or correspond to the functional state and activity of the entire brain (perhaps of the entire organism) and that the state and activity of this system are characterized by emergent properties that cannot be reduced to or deduced from the properties of component systems.

The unity of self-representation in awareness (the conscious "I") is a significant feature of conscious experience. Mental-physical identity theory indicates that there is a corresponding physical concept which designates the same psychophysical referent. MacKay addressed this point, proposing that the unity of phenomenal consciousness depends on the functional integration of cerebral information flow patterns: "The brain-correlate of the *unity* of the conscious 'I' would be sought at the information level, in the topological unity of the internal organizing activity made possible by information-linkages between the participating brain-elements" (21, p. 1389). In a more recent paper (20), MacKay continued, "The correlate of conscious mental activity . . . would not be the neural activity in a specific anatomical location so much as the informational traffic at a specific level of the cerebral information flow system" (p. 293). The significance of the information flow approach is its emphasis on process and functional properties, enabling understanding to transcend the structural anatomic/biochemical categories according to which causal or correlational hypotheses are conventionally organized. This orientation suggests that while the brain may be described in terms of structural organization, psychological phenomena are more likely to correspond to descriptions of brain processes in terms of functional organization, which reflect states and properties of the whole brain as a system.

Much of the mind-body literature related to emergence is focused on the idea of mind emerging from brain—a confusion of logical/categorial types, as noted earlier. Emergence within a particular conceptual network (mental or physical), however, remains a critical feature of organic unity theory. The significance of this for neuroscience was noted by computer scientist Douglas Hofstadter (29): "Godel's proof suggests that there could be some high-level way of viewing the mind/brain, involving concepts which do not appear on lower levels, and that this level might have explanatory power that does not even exist—not even in principle—on lower levels. It would then mean that some facts could be explained on the high level quite easily, but not on lower levels at all" (p. 708). It seems that reductionistic research and theories concerning neurochemistry and anatomic localization of function are unlikely to elucidate the more integrated and emergent physical processes which correspond to psychological phenomena and that there needs to be a complementary body of research and theory which focuses on the more integrated, emergent functioning of the brain as a whole.

The progress of physical science has both directly and indirectly fostered the development of new ways of understanding the function of the brain as a whole. Modern physics and electrodynamics enabled the development of positron emission tomography and nuclear magnetic resonance scanning, means by which the functioning of the whole brain may be studied in vivo. Indirectly, modern physical science has delineated patterns of functional relationships from which theoretical models of brain functioning may be generated by analogy. Current models of brain functioning are organized according to the conceptual relationships of classical (Newtonian) physics, which expresses an epistemological system as well as denoting a field of study. This epistemological system (theory of knowledge) is embodied in our linguistic and conceptual structures, imposing covert impediments to the development of new theories. It is proposed here that models elaborated through the use of conceptual structures and relationships developed in modern physics (including relativity, quantum mechanics, and chaos theory) may be able to provide understanding that is unavailable with current models. Maxwell (16) suggested that field theory could provide a model for understanding the configurational properties of nervous system functioning which correspond to the properties of psychological states and processes. Others, including Pribram et al. (30), Wolf (31), Bohm (32), and Pelletier (33, 34), have applied concepts from modern physics in developing provocative models of brain functioning.

The implications of organic unity theory for research are not limited to neuroscience and indicate that the appropriate domain for scientific research in psychiatry extends to other realms of data. According to organic unity theory, mental concepts and the corresponding physical concepts have the same referents although they belong to separate conceptual networks. Hence, the facts represented by phenomenal terms and those represented by physiological or behavioral terms have equivalent logical and epistemological status. The data of introspection are therefore no less valid for scientific inquiry than are physiological or behavioral data.

A further, more radical conclusion is suggested by the earlier discussion regarding the distinction between mental and physical concepts in terms of different forms of knowledge or ways of knowing. It may be recalled that a mental concept represents direct knowledge, by acquaintance (first-order access), of the intrinsic nature of an event, while the corresponding physical concept represents knowledge, by description (second-order access), of the causal/structural relationships of that same event. While all areas of science assert the existence of intrinsic properties and describe their causal/structural relationships, only in the case of introspective awareness (the "inward self-expression" of the mind-brain) can intrinsic properties be known directly by acquaintance. As stated by Globus (35), "If consciousness is literally identical with events, which to an observer are neurally embodied, then consciousness is literally the most direct manner of knowing these events" (p. 168). It may be noted that "most direct" is not necessarily equivalent to "best," since the significance of knowledge is a function of its relationship to other concepts in the conceptual network. The practical value of knowledge in the mental conceptual network will additionally depend on the number and strength of empirical identifications between physical concepts and mental concepts and the relational proximity within the conceptual network between these (identified) mental concepts and the knowledge in question.

Additional points relevant to research concern the hazards involved in mixing terms from conceptual systems of different logical or categorial types. Hypotheses that causally link events or processes described in physical terms with events or processes described in mental terms are particularly susceptible to dualistic fallacies.

### *Clinical Practice*

It is in the clinical practice of psychiatry that the inherent unity of the processes to which mental and physical terms refer is most readily experienced, though not so easily verbalized. The implications of organic unity theory for clinical practice may be considered in terms of general approach, diagnosis, and treatment.

*General approach.* The most evident implication of organic unity theory is that the dispute between physiological psychiatry and psychological or psychotherapeutic psychiatry serves no useful purpose. Each constitutes a valid conceptual framework and approach to assessment and treatment. In each system are some hypotheses and methods that are more valid and some that are less valid, according to the criteria for validity defined within that system. Clinicians provide the best care for their patients to the extent that they are able to approach, conceptualize, and relate to them as whole organic unities. It may not always be necessary for clinicians to be experts in the theory and practice of both pharmacotherapy and psychotherapy, but it is incumbent upon them to be fluent in both physical and mental languages and to appreciate and have the ability to evaluate both objective and subjective data. The energy that is currently being expended in polemics about whether physiological or psychological treatment is better would be more productively invested in attempting to delineate the conditions under which each approach is maximally effective.

*Diagnosis.* The implications of organic unity theory for psychiatric diagnosis begin with the recognition that a diagnostic system may be formulated in accordance with a physical (objective) conceptual network, a mental (subjective) conceptual network, or a combination of the two. A combination is likely to lead to confusion on logical as well as factual levels. The currently prevalent system represents an attempt to formulate diagnoses in the objective terms of the physical conceptual network. The value of this diagnostic system in organizing objective data and predicting responses to physiological interventions does not, however, preclude the possibility that a diagnostic system formulated in mental terms may be of comparable value in organizing subjective data and predicting responses to psychological interventions. Other implications for diagnosis relate to how the diagnostic system is to be organized. The discussion in the preceding section on the implications for psychiatric theory suggests that the division of psychiatric disorders into clinical syndromes (axis I in *DSM*) and personality disorders (axis II) may need to be reassessed. It is clear that the principles according to which a diagnostic system is organized must subserve pragmatic values in terms of predicting course of illness, prognosis, and response to treatment. It is often less clear how these principles reflect an underlying theoretical orientation. It is necessary to articulate this theoretical base as clearly and explicitly as possible so as to guard against the possibility that theoretical influences operating outside of awareness may undermine the pragmatic value of the system. Organic unity theory is proposed as a theoretical base from which a pragmatically valuable diagnostic system may be derived.

*Treatment.* Organic unity theory states that the events and processes with which psychiatry is concerned are both physical and mental and that the distinction resides not in the events and processes but in the linguistic/conceptual framework used in referring to them. This applies to therapeutic interventions as well as to the targets of interventions. "Physiological" or "psychological" interventions lead to changes in the organism that are both physical and mental, i.e., potentially describable in both physical and mental terms. It follows that there is no contradiction in describing psychotherapy as a biological treatment (36) and that a treatment philosophy which denies the significance of either physical or mental processes deserves to be viewed with suspicion. Organic unity theory implies that boundaries between treatment disciplines are arbitrary (although not thereby without value) and promotes enhanced openness between clinicians with different areas of expertise, as well as within a single clinician, toward diverse areas of study.

## CONCLUSIONS

In *The Structure of Scientific Revolutions*, Kuhn (37) wrote, "Something like a paradigm is prerequisite to perception itself. What a person sees depends both upon what he looks at and also upon what his previous visual-conceptual experience has taught him to see" (p. 113). This is no less true in the mental sciences than in the physical sciences, and it is particularly applicable to the science of psychiatry, which unites the mental and the physical, both as objects of inquiry and as modes of inquiry. Throughout this discussion it has been assumed that a significant relationship exists between physiology, psychology, and philosophy, which converge in psychiatry. It is hoped that the organic unity theory will promote actualization of the vast potential of this relationship.

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# Comorbidity of Attention Deficit Hyperactivity Disorder With Conduct, Depressive, Anxiety, and Other Disorders

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*Objective:* *Attention deficit hyperactivity disorder is a heterogeneous disorder of unknown etiology. Little is known about the comorbidity of this disorder with disorders other than conduct. Therefore, the authors made a systematic search of the psychiatric and psychological literature for empirical studies dealing with the comorbidity of attention deficit hyperactivity disorder with other disorders.* *Data Collection:* *The search terms included hyperactivity, hyperkinesis, attention deficit disorder, and attention deficit hyperactivity disorder, cross-referenced with antisocial disorder (aggression, conduct disorder, antisocial disorder), depression (depression, mania, depressive disorder, bipolar), anxiety (anxiety disorder, anxiety), learning problems (learning, learning disability, academic achievement), substance abuse (alcoholism, drug abuse), mental retardation, and Tourette's disorder.* *Findings:* *The literature supports considerable comorbidity of attention deficit hyperactivity disorder with conduct disorder, oppositional defiant disorder, mood disorders, anxiety disorders, learning disabilities, and other disorders, such as mental retardation, Tourette's syndrome, and borderline personality disorder.* *Conclusions:* *Subgroups of children with attention deficit hyperactivity disorder might be delineated on the basis of the disorder's comorbidity with other disorders. These subgroups may have differing risk factors, clinical courses, and pharmacological responses. Thus, their proper identification may lead to refinements in preventive and treatment strategies. Investigation of these issues should help to clarify the etiology, course, and outcome of attention deficit hyperactivity disorder.*

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Attention deficit hyperactivity disorder is a heterogeneous disorder of unknown etiology. The prevalence of the disorder has been estimated to range from 2% (1) in primary care pediatric samples to 6% (2) and 9% (3) in large-scale population studies of school-age children. Attention deficit hyperactivity disorder is one of the most common sources of referrals to family physicians, pediatricians, pediatric neurologists, and child psychiatrists. Its impact on society is enormous in terms of financial cost, stress to families, disruption in schools, and the potential for leading to criminality and substance abuse (4).

In recent years, evidence has been accumulating regarding high levels of comorbidity of attention deficit hyperactivity disorder with a number of disorders, including mood and anxiety disorders as well as conduct disorder. This high level of comorbidity has been found in culturally and regionally diverse epidemiologic samples (i.e., New Zealand and Puerto Rico) (2, 3, 5) as well as in clinical samples (6), indicating that attention deficit hyperactivity disorder is most likely a group of conditions with potentially different etiologic and modifying risk factors and different outcomes rather than a single homogeneous clinical entity.

Comorbidity raises fundamental questions as to whether psychiatric disorders are discrete and independent disease entities (7). Comorbidity pervasively affects research and clinical practice as a result of its influence on diagnosis, prognosis, treatment, and health care delivery (8). From the research perspective, subgroups of patients with attention deficit hyperactivity disorder and comorbid disorders may represent more homogeneous subgroups of patients with attention deficit hyperactivity disorder. From the clinical perspective, subgroups of patients with attention deficit hyperactivity disorder and comorbid disorders may respond differentially to specific therapeutic approaches. From the public health perspective, such subgroups may be at high risk for the development of severe psychopathology. Subgrouping children with

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attention deficit hyperactivity disorder may permit the development of early intervention strategies. This latter aspect is particularly important in the light of long-term follow-up studies of children with attention deficit hyperactivity disorder (9, 10), which indicate that a subgroup of subjects with attention deficit hyperactivity disorder and comorbid disorders have a poorer outcome as evidenced by significantly greater social, emotional, and psychological difficulties. Although the comorbidity of psychiatric disorders has been studied in adult psychiatry as a topic of major practical and theoretical significance (11), research data on attention deficit hyperactivity disorder have only recently been analyzed with comorbidity taken into account. Therefore, it remains to be determined whether research findings previously reported in children with attention deficit hyperactivity disorder are related to the attention deficit hyperactivity disorder itself, the existence of comorbid disorders, or the combination of both (12).

Several competing hypotheses have been proposed to account for patterns of comorbidity (12): 1) the comorbid disorders do not represent distinct entities but, rather, are the expression of phenotypic variability of the same disorder, 2) each of the comorbid disorders represents distinct and separate clinical entities, 3) the comorbid disorders share common vulnerabilities (13), either genetic (genotype), psychosocial (adversity), or both, 4) the comorbid disorders represent a distinct subtype (genetic variant) within a heterogeneous disorder (13) (i.e., attention deficit hyperactivity disorder plus conduct disorder may be a subtype of attention deficit hyperactivity disorder), 5) one syndrome is an early manifestation of the comorbid disorder (i.e., attention deficit hyperactivity disorder is an early manifestation of a conduct or mood disorder), and 6) the development of one syndrome increases the risk for the comorbid disorder (i.e., attention deficit hyperactivity disorder increases the risk for conduct or mood disorder). Investigation of these issues should help to clarify the etiology, course, and outcome of attention deficit hyperactivity disorder.

The development of a conceptual model for understanding the high rate of comorbidity of other disorders in attention deficit hyperactivity disorder is complicated by controversy regarding the validity of attention deficit hyperactivity disorder itself as a distinct clinical entity. Disagreements remain as to which of the multiple symptom domains represented in the criteria for attention deficit hyperactivity disorder should be viewed as constituting the core deficit (i.e., inattentiveness versus hyperactivity), the categorical or typological nature of the medically dominated diagnostic system versus a dimensional approach to classification, and whether pervasive or situational symptoms should be required for diagnosis. For example, a number of authorities have argued that evidence for the validity of attention deficit hyperactivity disorder is limited to a rather severe or pervasive type of the disorder (14–17). Despite this controversy, however, an extensive body of literature derived from longitudinal follow-up studies (10, 18, 19), treatment studies (20), psychosocial and developmental correlates (21), and family-genetic studies of male (6, 22) and female (23) probands support the concurrent and predictive validity of the broad conceptualization of attention deficit hyperactivity disorder as proposed in *DSM-III* and *DSM-III-R*.

Despite the thousands of scientific articles and the many review articles, books, and book chapters on attention deficit hyperactivity disorder in the medical, psychological, and educational literature, little is known about the comorbidity of this disorder with other disorders. This review examines the available literature on the extent and importance of comorbidity with other disorders in the syndrome of attention deficit hyperactivity disorder. We conducted a systematic search of the psychiatric and psychological literature for empirical studies dealing with the comorbidity of attention deficit hyperactivity disorder with other disorders. The search terms included hyperactivity, hyperkinesis, attention deficit disorder, and attention deficit hyperactivity disorder, cross-referenced with antisocial disorder (aggression, conduct disorder, antisocial disorder), depression (depression, mania, depressive disorder, bipolar), anxiety (anxiety disorder, anxiety), learning problems (learning, learning disability, academic achievement), substance abuse (alcoholism, drug abuse), mental retardation, and Tourette's disorder. Since citation of every published article on this topic is beyond the scope of this review, we selected for citation representative studies that were conducted with the most sophisticated methods. Although the *DSM-III-R* definitions of attention deficit hyperactivity disorder and related disorders anchor this review, many of the studies described here used other means of classification, including *DSM-II, DSM-III* attention deficit disorder, and dimensional descriptions of clinical syndromes. For simplicity of exposition, the names of *DSM-III-R* categories will be used generically unless otherwise specified.

## COMORBIDITY WITH CONDUCT DISORDER

Attention deficit hyperactivity disorder and conduct disorder have been found to occur together in 30% to 50% of cases in both epidemiologic (2, 3) and clinical (6, 24–34) samples (table 1). Whether attention deficit hyperactivity disorder and conduct disorder constitute separate symptom domains or diagnostic categories has been the topic of considerable debate (7, 35, 36, 40, 47–49; unpublished 1989 paper by B.B. Lahey and C.L. Carlson).

Two central positions concerning the relationship between attention deficit hyperactivity disorder and conduct disorder can be identified: attention deficit hyperactivity disorder and conduct disorder are indistinguishable (complete overlap), or they are either partially or completely independent. The position that

**TABLE 1. Representative Studies of Comorbid Attention Deficit Hyperactivity Disorder and Conduct Disorder**

| | | Subjects | | | | |
|---|---|---|---|---|---|---|
| Author | Year | Age (years) | Sex | N | Type | Type of Study and/or Comparison[a] |
| Offord et al. (35) | 1979 | 12[b] | M | 66 | Court cases | CD vs. ADD+CD |
| Lahey et al. (36) | 1980 | 8–11[d] | M, F | 109 | Nonreferred schoolchildren | —[c] |
| Sandberg et al. (37) | 1980 | 5–9[d] | M | 226 | Community sample | ADDH vs. CD |
| Prinz et al. (29) | 1981 | 6–8[d] | M, F | 109 | Schoolchildren rated hyperactive by teachers | Hyperactivity vs. hyperactivity+aggressive symptoms |
| Stewart et al. (25) | 1981 | 9[b] | M | 175 | Clinically referred | ADDH vs. CD vs. ADDH+CD |
| August et al. (38) | 1983 | Children | M | 52 | Clinically referred | Follow-up study; hyperactivity vs. hyperactivity+CD |
| August and Stewart (39) | 1983 | 5–13[d] | M | 67 | Clinically referred to child psychiatry; given diagnosis of hyperactivity | ADD with vs. without family history of antisocial disorder |
| Thorley (40) | 1984 | 5–11[d] | M, F | 146 | Clinically referred and control | Prospective longitudinal study; hyperactivity vs. CD |
| Gittelman et al. (18) | 1985 | 16–23[d] | M | 201 | Referred for hyperactivity; normal control | Prospective longitudinal follow-up study; hyperactive vs. control |
| McGee et al. (5) | 1985 | 9[b] | M, F | 926 | Community sample | Epidemiologic study |
| Weiss et al. (10) | 1985 | 21–33[d] | M, F | 104 | Referred; control | Prospective 15-year follow-up study; hyperactive vs. control |
| Shapiro and Garfinkel (27) | 1986 | 7–12[d] | M, F | 315 | Nonreferred schoolchildren | Epidemiologic study |
| Taylor et al. (15) | 1986 | 6–10[d] | M | 60 | Clinically referred for antisocial or disruptive behavior | Cluster analysis |
| Taylor et al. (16) | 1986 | 6–10[d] | M | 64 | Clinically referred for antisocial or disruptive behavior | —[c] |
| Anderson et al. (2) | 1987 | 11[b] | M, F | 792 | Nonreferred; subset of 53 given diagnosis of ADD | Epidemiologic study |
| Biederman et al. (24) | 1987 | 6–17[d] | M | 42[e] | Clinically referred; normal control | Family study; ADD vs. ADD+OPD vs. control |
| Loney (31) | 1987 | —[c] | —[c] | —[c] | Review of previous work | —[c] |
| Milich et al. (34) | 1987 | 6–12[d] | M | 76 | Clinically referred | Follow-up; ADD vs. CD vs. ADD+CD vs. other diagnoses |
| Reeves et al. (41) | 1987 | 5–12[d] | M, F | 105 | Referred | ADDH vs. ADDH+CD vs. anxiety vs. control |
| Bird et al. (3) | 1988 | 4–16[d] | M, F | 386 | Probability sample from population of Puerto Rico | Two-stage epidemiologic study |
| Klorman et al. (42) | 1988 | 6–12[d] | M, F | 63 | Referred to pediatrics, neurology, or psychiatry | Methylphenidate vs. placebo; ADHD vs. ADHD+aggressive symptoms vs. borderline ADHD |
| Lahey et al. (43) | 1988 | 6–13[d] | M, F | 86 | Outpatients referred for psychological assessment | Family study; ADHD vs. ADHD+CD vs. CD vs. control |
| Loeber et al. (19) | 1988 | —[c] | M | 187 | Volunteers in 4th, 7th, and 10th grades | Follow-up study; ADD+CD vs. ADD vs. CD vs. remainder |
| Barkley et al. (44) | 1989 | 6–13[d] | M, F | 74 | Clinically referred | Drug study; ADHD with vs. without aggressive symptoms |
| Farrington et al. (45) | 1989 | 8–25[d] | M | 411 | Nonreferred schoolchildren | Prospective longitudinal study |
| Lahey and Carlson (unpublished) | 1989 | 6–13[d] | M, F | 103 | —[c] | Review; ADDH vs. ADD |
| Mannuzza et al. (4) | 1989 | 16–23[d] | M | 372 | Clinically referred; control | Follow-up study |
| Szatmari et al. (21) | 1989 | 4–16[d] | M, F | 2,697 | Nonreferred | Epidemiologic study |
| Faraone et al. (46) | 1991 | 6–17[d] | M | 125 | Clinically referred; normal control | Family study; ADD vs. psychiatric control vs. normal control; ADD+CD vs. ADD+OPD vs. ADD |

[a] ADD=attention deficit disorder, ADHD=attention deficit hyperactivity disorder, ADDH=attention deficit disorder with hyperactivity, CD=conduct disorder, OPD=oppositional disorder.

[b] Mean.

[c] Information not provided.

[d] Range.

[e] Number of families rather than number of subjects.

**TABLE 1 (continued)**

| Instruments Used | Findings[a] |
|---|---|
| —[c] | More perinatal events in ADD+CD; no differences on other measures of psychosocial disadvantage or cognitive skills |
| Behavior checklists, achievement tests, peer rating scales | High intercorrelations for hyperactivity and conduct problem scale factors, similar correlation patterns for criterion variables; similar multiple regressions for combined and separate factors |
| —[c] | No differences |
| Rating scales | Positive correlation between hyperactive and aggressive symptoms; hyperactivity and aggressive symptoms intertwined |
| Clinical assessment, rating scales | No differences in age, IQ, and family size; more school problems in ADDH |
| Structured interviews, behavior checklists, achievement tests | At follow-up hyperactive children still inattentive and impulsive; those with hyperactivity+CD still inattentive, impulsive, aggressive, noncompliant, antisocial, and abusing alcohol |
| Clinical assessments, clinical interviews, WISC-R | ADD with family history of antisocial diagnosis significantly higher on aggression, noncompliance, antisocial behavior, egocentricity; significantly higher rate of CD in siblings |
| Clinical rating sheets (*ICD-9*), factor scales | CD had greater frequency of aggressive, antisocial, emotional, and psychosocial disturbances; hyperactive had greater frequency of hyperactivity and inattention |
| Structured interviews | Full ADDH in 31% of hyperactive vs. 3% of control; CD and substance use disorder significantly higher in hyperactive |
| Teacher ratings | ADDH ratings correlated with cognitive skills; no differences on psychosocial disadvantage; inattention correlated with cognitive skills; CD and hyperactivity correlated with psychosocial disadvantage |
| Structured interviews, self-rating scales, psychiatric histories (*DSM-III*) | 66% of hyperactive continued to have one or more disabling symptoms; 23% of hyperactive vs. 2.4% of control had antisocial personality disorder |
| Teacher ratings, structured interview, attentional battery, achievement tests | 2.3% had ADD; 3.6% had CD; 3.0% had ADD+CD; interdependence between ADD and CD |
| Behavior checklists, psychiatric interviews | 25% had high scores on hyperactivity and inattention; good response to stimulants; classification of pervasive hyperactivity with inattention robust |
| Semistructured interviews, behavior checklists, psychological testing | Independence of inattentive and antisocial, defiant, CD dimensions |
| Structured interviews, behavior checklists | 47% of ADD had CD and/or OPD; 35% of CD and/or OPD had ADD |
| Clinical interviews, structured interviews | 64% of ADD had CD and/or OPD; 46% of ADD+CD/OPD relatives vs. 13% of ADD relatives vs. 7% of control relatives had antisocial disorders |
| —[c] | Aggressive symptoms differentiated hyperactive/minimal brain dysfunction boys on several measures; differentiation between hyperactivity+aggressive symptoms and hyperactivity valuable |
| Structured interviews, statistical analysis of individual ADD and CD symptoms | Conditional probability of ADD in CD was 0.67; conditional probability of CD in ADD was 0.30; ADD and CD are partially independent |
| Structured interviews, cognitive tests, behavior questionnaires | 52% had two or more diagnoses; 85% of CD had ADD; ADDH and CD are partially independent |
| Behavior checklists, structured interviews | 57% of ADD had CD and/or OPD; 47% of CD and/or OPD had ADD |
| Achievement test, rating scales | Similar responses to methylphenidate in all three groups |
| Structured interviews, rating scales | Higher rates of aggression, arrest, and imprisonment in fathers of ADHD+CD; familiality of ADD not reported |
| Behavior and health checklists, intelligence tests, psychosocial assessment, police reports | Highest rates of police contacts and self-reported delinquency in ADD+CD; 30.8% of ADD+CD vs. 3.4% of ADD vs. 20.7% of CD vs. 1.7% of remainder were multiple offenders |
| Parental interview, behavior rating scales, cognitive tests | Aggressive and nonaggressive ADHD similar in drug responses; aggressive had more impaired family situations |
| Behavior checklist, cognitive assessments, criminal records | Hyperactivity and CD independently predictive of juvenile convictions; 45.8% of hyperactive+CD vs. 35% of CD vs. 23.5% of hyperactive vs. 12.6% with neither were convicted as juveniles |
| Structured interviews, rating scales | 41% of ADDH vs. 20% of ADD had CD |
| Structured interviews | For cohort 1, 68% of ADD vs. 13% of control had ADD and 45% of ADD vs. 16% of control had CD; for cohort 2, 70% of ADD vs. 10% of control had ADD and 59% of ADD vs. 18% of control had CD |
| Structured interviews, behavior checklists, clinical diagnoses | ADD and CD occurred together significantly often; ADD+CD seemed true hybrid disorder |
| Structured interviews, morbidity risk | Higher familial risk for ADD, antisocial disorders, and substance use disorder in ADD+CD; earlier age at onset of ADD and highest rates of school dysfunction in ADD+CD; ADD+CD had more virulent form of ADD; OPD was familial (validity of OPD); ADD+OPD was intermediate between ADD and ADD+CD (OPD may be subsyndromal manifestation of CD) |

attention deficit hyperactivity disorder and conduct disorder are indistinguishable suggests that, given the measurement and/or diagnosis of either attention deficit hyperactivity disorder or conduct disorder, the identification of the other yields no additional information. Proponents of this position point to the similarities between children with attention deficit hyperactivity disorder and children with conduct disorder frequently reported in studies of correlates, outcome, and treatment responses (44, 50). Similarly, they point to intercorrelations between symptoms of attention deficit hyperactivity disorder and symptoms of conduct disorder (aggressive, disruptive, and noncompliant behaviors) often reported in factor-analytic studies of children with behavioral disorders (51, 52). In addition, they cite a lack of substantial differences in psychosocial, neurodevelopmental, and perinatal factors between children with attention deficit hyperactivity disorder and children with conduct disorder (37).

Proponents of the independent position view attention deficit hyperactivity disorder and conduct disorder as either completely or partially independent. Support for this position can be derived from studies that compared patterns of familial aggregation, cognitive performance, and outcome of children with attention deficit hyperactivity disorder with those of children with attention deficit hyperactivity disorder plus conduct disorder. In the studies of Loney et al. (53), symptoms of hyperactivity and aggression were not highly correlated and showed different patterns of concurrent and predictive validity, suggesting that they were separate dimensions. In those studies, the presence of conduct disorder in childhood, whether associated with attention deficit hyperactivity disorder or not, was significantly correlated with aggressive behavior and delinquency in adolescence (53), but childhood attention deficit hyperactivity disorder without conduct disorder was correlated with cognitive and academic deficits (21, 32, 54). Similar findings emerged from a follow-up study in a nonclinical sample (55, 56). Other studies (21, 34, 38, 41, 45, 57, 58) have demonstrated that children with attention deficit hyperactivity disorder with an associated childhood-onset conduct disorder have more serious clinical courses and poorer outcomes than children with attention deficit hyperactivity disorder without conduct disorder.

Family studies have shown that childhood conduct disorder, but not attention deficit hyperactivity disorder, is associated with parental antisocial behaviors and alcoholism (6, 25, 38, 46, 54). Investigators have found that the familial risk for attention deficit hyperactivity disorder and antisocial disorders is highest among relatives of children with attention deficit hyperactivity disorder with concomitant conduct disorder (24, 28, 46, 54, 59). Several reports have also shown that a current or past history of attention deficit hyperactivity disorder is frequently reported among patients with alcohol dependence (60–62) and drug addiction (63, 64). Since follow-up studies of children and adolescents with the diagnosis of conduct disorder are in agreement regarding the strong predictive power of conduct disorder for future psychiatric disorders, social adjustment problems, antisocial personality, alcoholism, and criminality (58), it has been suggested that the delinquent behaviors and substance abuse often reported in follow-up studies of boys with attention deficit hyperactivity disorder (18, 65) may be linked to childhood antisocial disorders rather than to the syndrome of attention deficit hyperactivity disorder per se (4, 39, 45).

Two studies examining the response to stimulants of children with attention deficit hyperactivity disorder with and without associated conduct disorder (42, 44) found that the two groups of children showed similar patterns of improvement with regard to symptoms of attention deficit hyperactivity disorder. Although these two studies cannot help resolve the debate regarding the independence of attention deficit hyperactivity disorder and conduct disorder, they support the clinical relevance of diagnosing both attention deficit hyperactivity disorder and conduct disorder when the disorders occur together.

Although debate continues as to whether attention deficit hyperactivity disorder is distinct from conduct disorder, the bulk of the evidence appears to indicate that attention deficit hyperactivity disorder and conduct disorder are at least partially independent dimensions and/or categories. Attention deficit hyperactivity disorder and conduct disorder differ not only in their defining clinical features but also in external variables such as outcome (cognitive dysfunction for attention deficit hyperactivity disorder versus aggression, antisocial behaviors, substance abuse, and delinquency for conduct disorder), etiologic factors (familial aggregation), and psychosocial and developmental correlates. Thus far, data from treatment studies have not resolved the debate. There is increasing evidence that children with attention deficit hyperactivity disorder plus conduct disorder appear to have a particularly severe form of attention deficit hyperactivity disorder. Thus, subgrouping based on comorbidity with conduct disorder may be of potential value in determining which children with attention deficit hyperactivity disorder have a more serious prognosis and different family-genetic risk factors and require specialized comprehensive therapeutic interventions.

## COMORBIDITY WITH OPPOSITIONAL DEFIANT DISORDER

The nosologic status of oppositional defiant disorder and consequently that of attention deficit hyperactivity disorder plus oppositional defiant disorder remains unclear (66, 67). To date, only a few studies have generated data on oppositional defiant disorder. Some of these have grouped oppositional defiant disorder and conduct disorder together into a single antisocial behavioral category, making it difficult to draw conclusions about oppositional defiant disorder itself. The few studies available report an overlap of at least 35% between attention deficit hyperactivity disorder and oppositional defiant disorder, either alone or combined with conduct disorder, in both epidemiologic (2, 3) and clinical (6, 46) studies of children and adolescents. Faraone et al. (46) recently demonstrated that *DSM-III* oppositional disorder itself is also familial and that the risk for oppositional disorder among relatives of probands with attention deficit disorder plus oppositional disorder is three times greater than the risk among relatives of probands with attention deficit disorder without oppositional disorder and nearly ten times greater than the risk among relatives of normal control subjects. These data provide some evidence for the validity of *DSM-III* oppositional disorder.

In terms of severity of the clinical picture, the available data suggest that children with attention deficit hyperactivity disorder plus oppositional defiant disorder may form an intermediate subgroup between those who have attention deficit hyperactivity disorder alone and those with attention deficit hyperactivity disorder plus conduct disorder. For example, Faraone et al. (46) showed that although probands with *DSM-III* attention deficit disorder plus oppositional disorder had a higher rate of school dysfunction than those with attention deficit disorder alone, this rate was lower than that of subjects with attention deficit disorder plus conduct disorder. A similar pattern was observed in the risk for attention deficit disorder and antisocial disorders among relatives of probands: family members of probands with attention deficit disorder plus oppositional disorder were at higher risk for antisocial disorders and attention deficit disorder than relatives of probands with attention deficit disorder alone but at lower risk than relatives of probands with attention deficit disorder plus conduct disorder. These findings are consistent with the hypothesis that oppositional defiant disorder may be a subsyndromal manifestation of conduct disorder (unpublished 1985 paper by J. Loney).

## COMORBIDITY WITH MOOD DISORDERS

Attention deficit hyperactivity disorder and mood disorders have been found to occur together in 15% to 75% of cases in both epidemiologic (2, 3) and clinical (6, 68–71) samples of children and adolescents (table 2). Some investigators, however, have not found higher-than-expected rates of mood disorders in children with attention deficit hyperactivity disorder (10, 18, 43, 72). In clinical samples, the association between attention deficit hyperactivity disorder and mood disorders has been reported in studies of children with nonbipolar major depression and dysthymia (75), studies of adolescents with bipolar disorder (80), and studies of children with attention deficit hyperactivity disorder (6, 69, 73, 77). Studies of high-risk children of parents with mood disorders have found high rates of attention deficit hyperactivity disorder in these children (78, 79; unpublished 1989 paper by H. Orvaschel), and family studies of children with attention deficit hyperactivity disorder have found a significantly higher rate of mood disorders in probands with attention deficit hyperactivity disorder and in their first-degree relatives than in normal control children and their first-degree relatives (74, 76). Studies of adopted children with the diagnosis of attention deficit hyperactivity disorder found higher rates of major depressive disorder in the biological relatives of these children than in their adoptive relatives and the biological relatives of control subjects (82). Case reports have described individuals with childhood histories of attention deficit hyperactivity disorder who developed major affective disorders in later years (83). It is doubtful that the comorbidity of attention deficit hyperactivity disorder and mood disorders can be explained by ascertainment bias because high levels of comorbidity of these disorders have also been found in culturally and regionally diverse population-based epidemiologic samples (2, 3, 5).

Findings reported by Biederman et al. (84) support the hypothesis that *DSM-III* attention deficit disorder and major depressive disorder share common familial vulnerabilities. Familial risk analyses revealed the following: 1) the risk for major depressive disorder among the relatives of probands with attention deficit disorder was significantly higher than the risk among relatives of normal comparison children, 2) the risk for major depressive disorder was the same among the relatives of probands with and without major depressive disorder and significantly higher in both groups than among the relatives of normal control children, and 3) the two disorders did not cosegregate within families. These findings are consistent with the hypothesis that attention deficit disorder and major depressive disorder represent different expressions of the same etiologic factors responsible for the manifestation of attention deficit disorder. The reasons why the shared genotype may have differing phenotypic expressions such as attention deficit disorder, major depressive disorder, or attention deficit disorder plus major depressive disorder remain unknown.

Follow-up data for children with attention deficit hyperactivity disorder as well as for children with major depressive disorder (85, 86) strongly suggest that although these disorders are individually associated with substantial long-term psychiatric morbidity, their occurrence together may be associated with a particularly poor outcome. In a study that evaluated predictors of suicide in adolescents, Brent et al. (87) reported that adolescents who committed suicide had higher rates of bipolarity and attention deficit hyperactivity disorder than did those who attempted suicide. Thus, the occurrence together of attention deficit hyperactivity disorder and mood disorder is suggestive of a subgroup of children with attention deficit hyperactivity disorder at higher risk for greater psychiatric morbidity and disability (81) and perhaps at higher risk for suicide than other children with attention deficit hy-

**TABLE 2. Representative Studies of Comorbid Attention Deficit Hyperactivity Disorder and Depression**

| | | Subjects | | | | |
|---|---|---|---|---|---|---|
| Author | Year | Age (years) | Sex | N | Type | Type of Study and/or Comparison[a] |
| Stewart and Morrison (72) | 1973 | Children | M, F | 135 | Clinically referred | Family study; biological ADD vs. adopted ADD vs. control |
| Staton and Brumback (68) | 1981 | 5–12[b] | M, F | 178 | Referred for school problems | —[c] |
| Bohline (73) | 1985 | 6–11[b] | M, F | 108 | Referred for special education | ADD vs. no ADD |
| Gittelman et al. (18) | 1985 | 16–23[b] | M | 201 | Referred for hyperactivity; normal control | Prospective longitudinal follow-up study; hyperactive vs. control |
| Weiss et al. (10) | 1985 | 21–33[b] | M, F | 102 | Referred hyperactive and normal control | Prospective longitudinal follow-up study |
| Anderson et al. (2) | 1987 | 11[d] | M, F | 792 | Nonreferred; subset of 53 given diagnosis of ADD | Epidemiologic study |
| Biederman et al. (74) | 1987 | 6–17[b] | M, F | 42[e] | Clinically referred for ADD and nonreferred control | Family study |
| Alessi and Magen (75) | 1988 | —[c] | —[c] | 160 | Clinically referred for MDD, dysthymia, or other diagnosis | Examination of comorbid disorders |
| Biederman et al. (76) | (in press) | 6–17[b] | M, F | 99[e] | Referred; pediatric control | Family study; ADD+MDD vs. ADD vs. control |
| Bird et al. (3) | 1988 | 4–16[b] | M, F | 386 | Probability sample from population of Puerto Rico | Two-stage epidemiologic study |
| Brown et al. (77) | 1988 | 6–12[b] | M, F | 116[e] | Referred; matched control | Family study; ADD vs. no ADD |
| Jensen et al. (70) | 1988 | 9–18[b] | M | 35 | Referred outpatients and control | MDD vs. ADDH vs. control |
| Keller et al. (78) | 1988 | 6–19[b] | M, F | 275 | Mixture of offspring of MDD parents and community sample of MDD and non-MDD parents | Retrospective assessment of course |
| Orvaschel et al. (79) | 1988 | 6–17[b] | M, F | —[c] | Children of referred unipolar parents and normal control parents | High-risk study; MDD vs. control |
| Strober et al. (80) | 1988 | 13–17[b] | M, F | 81 | Inpatients | Family study; bipolar I vs. schizophrenia |
| Lahey and Carlson (unpublished) | 1989 | 6–13[b] | M, F | 103 | —[c] | Review; ADD vs. ADDH |
| Mannuzza et al. (4) | 1989 | 16–23[b] | M | 372 | Clinically referred; control | Follow-up study |
| Weinberg et al. (81) | 1989 | 6–15[b] | M, F | 227 | All students in school for children with learning disabilities | ADD+MDD vs. ADD vs. MDD vs. chronic mood disturbance vs. no behavioral condition |
| Woolston et al. (71) | 1989 | 4–14[b] | M, F | 35 | Inpatients | Psychiatric assessments |

[a] ADD=attention deficit disorder, ADHD=attention deficit hyperactivity disorder, ADDH=attention deficit disorder with hyperactivity, CD=conduct disorder, MDD=major depressive disorder, OPD=oppositional disorder.

[b] Range.

[c] Information not provided.

[d] Mean.

[e] Number of families rather than number of subjects.

peractivity disorder and adolescents without such comorbid disorders.

## COMORBIDITY WITH ANXIETY DISORDERS

Epidemiologic (2, 3) and clinical samples of children with anxiety disorders (88) and children with attention deficit hyperactivity disorder (6, 43, 69, 71, 89) have found a comorbid association between attention deficit hyperactivity disorder and anxiety disorders of approximately 25% (table 3). Investigators have also noted higher rates of attention deficit hyperactivity disorder in children of parents with anxiety disorders than in children of comparison groups (91). Lahey et al. (43, 90) noted that children with a *DSM-III* diagnosis of attention deficit disorder without hyperactivity had higher rates of anxiety disorders than children with attention deficit hyperactivity disorder. A recent investigation of the familial interrelationship between attention deficit hyperactivity disorder and anxiety disorders (92) provided evidence for an association be-

**TABLE 2 (continued)**

| Instruments Used | Findings[a] |
|---|---|
| Interviews | No significant differences in rates of bipolar and unipolar affective disorder |
| Clinical assessments | 60% met criteria for MDD; 44% met criteria for hyperactivity; 73% of hyperactive had MDD; 55% of MDD had hyperactivity |
| Questionnaires | ADD more depressed than no ADD |
| Structured interviews | 3% of hyperactive vs. 2% of control had current affective disorder; 6% of hyperactive vs. 10% of control had history of affective disorder |
| Structured interviews, self-rating scales, psychiatric histories (*DSM-III*) | More suicide attempts by hyperactive than control in year before follow-up; no significant differences in depression scores on self-rating scale |
| Structured interviews, behavior checklists | 15% of ADD met criteria for depression and/or dysthymia; 57% of MDD met criteria for ADD |
| Structured interviews | 32% of ADD and 27% of ADD relatives met criteria for MDD vs. none of control and 6% of control relatives |
| Interviews | 25% of ADD, 25% of CD, and 25% of anxious had MDD; 22% of ADD, 33% of CD, and 89% of anxious had dysthymia |
| Structured interviews | 26% of ADD probands had MDD; morbidity risks for ADD and MDD in ADD and ADD+MDD differed significantly from control |
| Behavior checklists, structured interviews | 19% of ADD met criteria for MDD; 30% of MDD met criteria for ADD |
| Depression inventory | ADD and ADD parents were significantly more depressed than no ADD and no ADD parents |
| Rating scales, structured interviews | Rates of specific disorders not reported; significant symptom (externalizing) overlap between ADD and MDD; few ADD symptoms in MDD boys but high rates of externalizing behaviors and impulsivity and low frustration tolerance (question of OPD); depressive symptoms commonly noted in ADDH boys (question of dysthymia) |
| Structured interviews | 14% had MDD; 87% had at least one MDD parent; 53% had anxiety, ADD, CD, or substance use disorder; 29% had two or more comorbid diagnoses; 45% with two or more diagnoses had ADD |
| —[c] | High rates of MDD and ADD in children of MDD parents |
| Structured interviews, RDC | 24% of adolescent bipolar I probands had childhood history of ADDH; rate of ADDH in relatives not reported |
| —[c] | 9% of ADDH vs. 8% of ADD had MDD (n.s.) |
| Structured interviews | No case of current major depression in ADD; lifetime (since age 13) prevalence of MDD not significantly different between ADD and control |
| Standardized psychometric intelligence and achievement tests, semistructured interviews | ADD+MDD had most behavioral problems |
| Clinical diagnoses, behavior checklists, intelligence tests | 32% had ADHD with dysthymia |

tween the two disorders. This study found 1) that the risk for anxiety disorders among the relatives of patients with attention deficit hyperactivity disorder was significantly higher than the risk among relatives of normal comparison children, 2) that the risk for anxiety disorders was significantly higher in relatives of probands with attention deficit hyperactivity disorder and anxiety disorders than in relatives of children with attention deficit hyperactivity disorder without anxiety disorders, and 3) that nonindependent transmission of attention deficit hyperactivity disorder and anxiety disorders within families could not be established. These findings suggest that attention deficit hyperactivity disorder and anxiety disorders transmit independently in families.

## COMORBIDITY WITH LEARNING DISABILITIES

An overlap between attention deficit hyperactivity disorder and learning disabilities has been consistently reported in the literature. The reported degree of over-

**TABLE 3. Representative Studies of Comorbid Attention Deficit Hyperactivity Disorder and Anxiety**

| Author | Year | Subjects |  |  |  | Type of Study and/or Comparison[a] |
|---|---|---|---|---|---|---|
|  |  | Age (years) | Sex | N | Type |  |
| Gittelman et al. (18) | 1985 | 16–23[b] | M | 201 | Referred hyperactive and normal control | Prospective longitudinal follow-up study; hyperactive vs. control |
| Anderson et al. (2) | 1987 | 11[c] | M, F | 792 | Nonreferred; subset of 53 given diagnosis of ADD | Epidemiologic study |
| Lahey et al. (90) | 1987 | 6–13[b] | M, F | 63 | Clinically referred; given diagnosis of ADD | ADDH vs. ADD |
| Last et al. (88) | 1987 | 5–18[b] | M, F | 73 | Outpatients at anxiety clinic | Assessment of comorbidity |
| Munir et al. (69) | 1987 | 5–16[b] | M | 42 | Clinically referred; pediatric control | Family study |
| Sylvester et al. (91) | 1987 | 7–17[b] | M, F | 91 | High-risk children of anxious, depressed, or control parents | Comparison of three structured interviews |
| Bird et al. (3) | 1988 | 4–16[b] | M, F | 386 | Probability sample from population of Puerto Rico | Two-stage epidemiologic study |
| Mannuzza et al. (4) | 1989 | 16–23[b] | M | 372 | Clinically referred; control | Follow-up study |
| Pliszka (89) | 1989 | —[d] | M, F | 79 | Clinically referred | Drug study |
| Woolston et al. (71) | 1989 | 4–14[b] | M, F | 35 | Inpatients | Psychiatric assessments |
| Biederman et al. (92) | 1991 | 6–17[b] | M, F | 125 | Clinically referred; pediatric control | Family study; ADD vs. psychiatric control vs. normal control |

[a] ADD=attention deficit disorder, ADHD=attention deficit hyperactivity disorder, ADDH=attention deficit disorder with hyperactivity, CD=conduct disorder.

[b] Range.

[c] Information not provided.

[d] Mean.

lap ranges from as low as 10% (57, 93) to as high as 92% (94). This variability is most likely due to differences in selection criteria, sampling, and measurement instruments, as well as inconsistencies in the criteria used to define both attention deficit hyperactivity disorder and learning disabilities in different studies (95, 96). In addition to these inconsistencies in the definitions of learning disabilities and attention deficit hyperactivity disorder, the academic dysfunction commonly associated with both conditions and the heterogeneity of the learning disabilities have led to widespread confusion about these disorders.

Studies have consistently shown that children with attention deficit hyperactivity disorder perform more poorly in school than control subjects, as evidenced by more grade repetitions, poorer grades in academic subjects, more placement in special classes, and more tutoring (94, 97–99). Findings also indicate that children with attention deficit hyperactivity disorder perform more poorly than control subjects on standard measures of intelligence and achievement (51). Follow-up studies have found that the academic and learning problems of children with attention deficit hyperactivity disorder persist into adolescence and are associated with chronic underachievement and school failure (10, 18). It is still unknown whether school failure in children with attention deficit hyperactivity disorder is related to the psychiatric picture of inattention and impulsivity (attention deficit hyperactivity disorder), cognitive deficits (learning disabilities), a combination of both factors (attention deficit hyperactivity disorder plus learning disabilities), or perhaps other factors such as social disadvantage or demoralization and consequent decline in motivation (51).

The finding in some studies that learning disabilities are almost universally found among children with attention deficit hyperactivity disorder (94) has led some authors to suggest that attention deficit hyperactivity disorder and learning disabilities may be indistinguishable (100). However, important differences exist in the defining characteristics of both disorders. Although attention deficit hyperactivity disorder is a behavioral syndrome with characteristic symptoms of inattentiveness, impulsivity, and hyperactivity, learning disabilities refer to a group of cognitive disorders thought to reflect perceptual handicaps in one or more basic cognitive processes manifested as disorders of language, reading, writing and spelling, or arithmetic. Moreover, many children with attention deficit hyperactivity disorder are achieving adequately, and not all children with learning disabilities have attention deficit hyperactivity disorder, suggesting that the two disorders may be independent but can overlap in some individuals (101).

In an attempt to clarify the nature of the association between attention deficit hyperactivity disorder and learning disabilities, researchers have begun to compare subgroups of children with learning disabilities, attention deficit hyperactivity disorder, and attention deficit hyperactivity disorder plus learning disabilities (93, 102). Although this approach holds promise, most studies have found few differences among subgroups.

**TABLE 3 (continued)**

| Instruments Used | Findings[a] |
|---|---|
| Structured interviews | None of hyperactive vs. 2% of control had current anxiety disorder; none of hyperactive vs. 3% of control had history of anxiety disorder |
| Structured interviews, behavior checklists | 26% of ADD had anxiety; 24% of anxious had ADD |
| Structured interviews, behavior checklists | 43% of ADD vs. 10% of ADDH had concurrent internalizing diagnosis |
| Semistructured interviews | 16.7% of those with separation anxiety had ADD; 18.2% of overanxious had ADD |
| Structured interviews | 27% of ADD vs. 15% of control had anxiety |
| Structured interviews, personality inventories | 33% with panic disorder parents vs. 6% with control parents had ADD according to child report; 43% with panic disorder parents had panic disorder by parent report; 40% with panic disorder parents had panic disorder by child report |
| Structured interviews, behavior checklists | 8% of ADD had anxiety; 18% of anxious had ADD |
| Structured interviews | Current anxiety disorders rare in ADD; lifetime (since age 13) prevalence of anxiety disorders not significantly different between ADD and control |
| Clinical interviews, observational measures, memory tests | 28% of ADHD had anxiety; ADHD+anxiety had significantly less CD than did ADHD; ADHD+anxiety had poorer response to methylphenidate than ADHD |
| Behavior checklists, IQ tests | 61% had ADHD+anxiety |
| Structured interviews | 30% of ADD vs. 15% of normal control had anxiety |

For example, Halperin et al. (93) compared children with attention deficit hyperactivity disorder plus learning disabilities (reading disabilities) with children with only attention deficit hyperactivity disorder to examine whether children with both disorders constitute a distinct subgroup. The authors interpreted their finding that the two groups did not differ behaviorally or in sociodemographic characteristics as giving minimal support to the usefulness of subgrouping attention deficit hyperactivity disorder on the basis of the presence of learning disabilities. In a study using a similar design and analytic approach, Ackerman et al. (102) also failed to find differences between children with comorbid attention deficit hyperactivity disorder and learning disabilities and children with attention deficit hyperactivity disorder alone on measures of impulsivity and response to stimulants. It is important to stress, however, that although the children in these studies all shared the clinical features of attention deficit hyperactivity disorder, they may have differed in fundamental ways determined by the presence of learning disabilities and its correlates. The identification of these differences may have major clinical and educational importance because the two disorders require different intervention approaches. Although more research is needed to further evaluate the nature of the association between attention deficit hyperactivity disorder and learning disabilities, the subgroup of children with attention deficit hyperactivity disorder plus learning disabilities deserves special clinical and educational attention.

## COMORBIDITY WITH OTHER DISORDERS

Attention deficit hyperactivity disorder is generally considered to be three to four times more prevalent in mentally retarded children than in those with normal IQ scores (103–106). In a study that analyzed the type of behavioral disturbance as a function of IQ (104), conduct disorder was found to be far more common than attention deficit hyperactivity disorder in boys with IQs greater than 50, but attention deficit hyperactivity disorder and conduct disorder were equally prevalent in children with IQs less than 50. In another study (103), attention deficit hyperactivity disorder was found to be much more common in the educable mentally retarded (IQ greater than 50) than in the general population. Russell (106) has noted that individuals with IQs less than 50 may exhibit different types of psychiatric disorders than those with milder mental retardation. In addition, studies in which stimulant treatment has been shown to be effective in children with attention deficit hyperactivity disorder plus mental retardation have been conducted only in subjects with mild mental retardation (107, 108). These data are consistent with a definition of attention deficit hyperactivity disorder that allows comorbidity with mild mental retardation but imposes an IQ cutoff below which attention deficit hyperactivity disorder should not be diagnosed. Since attention deficit hyperactivity disorder appears to occur with increasing frequency in individuals with mental retardation, more work needs to be done to evaluate whether attention and activity problems in the mentally retarded should be viewed as constituting attention deficit hyperactivity disorder or whether they are a consequence of having a low IQ.

Comorbidity of Tourette's syndrome and attention deficit hyperactivity disorder has been well documented. Approximately 60% of children and adolescents with Tourette's syndrome have been shown to have comorbid attention deficit hyperactivity disorder (13, 109–111). Because the prevalence of attention deficit hyperactivity disorder is much higher than that of Tourette's syndrome, only a small percentage of children with attention deficit hyperactivity disorder will have comorbid Tourette's syndrome. Although the comorbidity figures from these studies are in close agreement, discrepant viewpoints have been proposed regarding their interpretation. Comings and Comings (109, 111) contended that there is a genetic relationship between Tourette's syndrome and attention deficit hyperactivity disorder and that a Tourette's syndrome gene (as yet unidentified) accounts for approximately 10%–30% of attention deficit hyperactivity disorder. Conversely, Pauls et al. (13) disputed the conclusion that attention deficit hyperactivity disorder and Tourette's syndrome are genetically related. Identification of children at risk for the development of Tourette's syndrome within the larger population of individuals with attention deficit hyperactivity disorder has important practical implications because psychostimulant treatment has been associated with the development of Tourette's syndrome in some studies (112) and may be contraindicated in children at high risk for Tourette's syndrome.

Comorbidity of attention deficit hyperactivity disorder and borderline personality disorder has been described by Andrulonis et al. (113), who found that 25% of a group of 106 borderline patients with IQs greater than 80 had a current or past history of attention deficit hyperactivity disorder and/or learning disabilities. Similarly, Bellak et al. (114–116) described a group of subjects with impulsive behavior, learning problems, mood lability, impaired judgment, disorganization, and intermittently poor reality testing whom they referred to as having attention deficit hyperactivity disorder psychosis. Successful treatment of comorbid attention deficit hyperactivity disorder and borderline personality with methylphenidate (117) and imipramine (118) has been described in case reports.

## CONCLUSIONS

There is increasing recognition that attention deficit hyperactivity disorder is a heterogeneous disorder with considerable and varied comorbidity. The weight of the available literature indicates the frequent occurrence together of conduct, mood, and anxiety disorders, as well as learning disabilities, with attention deficit hyperactivity disorder in childhood, adolescence, and adulthood. The observed comorbidity does not appear to be either random or artifactual. Rather, specific patterns of symptoms and syndromes tend to occur together in individuals and families. Current research findings have begun to suggest that subgroups might be delineated on the basis of patterns of comorbidity. Recent family-genetic data suggest that attention deficit hyperactivity disorder plus conduct disorder may be a distinct subtype, that attention deficit hyperactivity disorder and major depression may share common familial vulnerabilities, and that attention deficit hyperactivity disorder and anxiety disorders may be independently transmitted. Ongoing research on attention deficit hyperactivity disorder and comorbid learning disabilities as well as other comorbid disorders will determine the nature of their association. Subgroups of patients with attention deficit hyperactivity disorder may have different risk factors, clinical courses, neurobiology, and pharmacological responses, so their proper identification may lead to refinements in prevention and treatment strategies. Although the high level of comorbidity within attention deficit hyperactivity disorder may lead to problems in differential diagnosis, these difficulties do not invalidate the diagnosis of the disorder. Rather, further examination of the patterns and structure of observed comorbidity could help to revise and improve existing methods of classification.

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# The Psychological Sequelae of Therapeutic Abortion—Denied and Completed

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*Objective: The purpose of this article is to review the available literature on the psychological sequelae of therapeutic abortion, addressing both the issue of the effects of the abortion on the woman involved and the effects on the woman and on the child born when abortion is denied. Method: Papers reviewed were initially selected by using a Medline search. This procedure resulted in 225 papers being reviewed, which were further selected by limiting the papers to those reporting original research. Finally, studies were assessed as to whether or not they used control groups or objective, validated symptom measures. Results: Adverse sequelae occur in a minority of women, and when such symptoms occur, they usually seem to be the continuation of symptoms that appeared before the abortion and are on the wane immediately after the abortion. Many women denied abortion show ongoing resentment that may last for years, while children born when the abortion is denied have numerous, broadly based difficulties in social, interpersonal, and occupational functions that last at least into early adulthood. Conclusions: With increasing pressure on access to abortion services in North America, nonpsychiatrist physicians and mental health professionals need to keep in mind the effects of both performing and denying therapeutic abortion. Increased research into these areas, focusing in particular on why some women are adversely affected by the procedure and clarifying the relationship issues involved, continues to be important.*

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After a period of relative quiescence, therapeutic abortion services are once again attracting significant political and public attention in North America and elsewhere. Systematic evaluation of any medical procedure usually requires examination of both the effects of performing that procedure and the effects on the patient when nothing is done. Despite a great deal of concern about the psychological effects of therapeutic abortion in both the lay and scientific press, the research examining either side of this issue, particularly that looking at the effects of denying abortion on the parent and child, is sparse.

The last half century has seen a trend toward progressively more liberal laws with respect to access to abortion, particularly in developed nations. Currently in the United States approximately 1.5 million therapeutic abortions are performed annually, involving 27.4 of every 1,000 women betwen the ages of 15 and 44. Worldwide, an estimated 30–40 million legal abortions are performed annually, with perhaps another 20 million illegal abortions (1). Recently, in North America, as well as in some European countries, we have seen a trend toward reexamination of this liberalization and reinstitution of more restrictive laws. Moreover, in the developing countries highly restrictive laws often persist, a situation that is complicated by "right-to-life" groups in Western nations that ally themselves with conservative forces in some developing nations to try to strengthen restrictive abortion laws there (2).

This paper has broken down the existing literature in order to address the following essential questions. The first is the simplest to address, and hence the one that has generated the most research interest. What are the psychological sequelae of therapeutic abortion, both the immediate effects and the more subtle, long-lasting effects? When abortion is denied, the issues are more varied. What proportion of women go on to find abortion elsewhere? If the fetus is not aborted, how many of the infants are actually adopted away, the alternative most often offered? Most importantly, what are the effects on the mother and the child when abortion is denied? Obviously, these are questions not easily addressed scientifically. There can be no random

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assignment of pregnant women to a group granted abortion and to one denied abortion. Follow-up, particularly for women denied abortion services, is understandably difficult. Cultural, social, and legal variations from place to place make comparability of studies difficult.

## PSYCHOLOGICAL SEQUELAE OF COMPLETED ABORTION

The first group to review systematically this particular side of the abortion issue was Simon and Senturia (3) in 1966; they commented on the wide range of results quoted by various studies, most of whose methodology they severely criticized. In 1981, Doane and Quigley (4) published an even more exhaustive review of the literature, also commenting on the large proportion of studies that were severely hampered by major methodologic flaws. They criticized in particular the lack of any control group and the fact that the majority of studies were impressionistic reports of a handful of cases. Other problems included short periods of follow-up, vague and poorly defined symptoms without objective measurement, low response rates, and unspecified indications for the abortion. The last problem is particularly significant in that it has been clearly demonstrated that medical or genetic indications for abortion increase the risk of adverse psychological sequelae in the mothers (5, 6).

Since those two reviews, research has continued in this area. The ongoing trend to liberalize abortion access laws toward the principle of abortion on demand has had an impact on research in this field. Early research tended to concentrate on psychiatric or medical complications of abortion, emphasizing a disease model, as some conception of disease was often required for abortion to be performed legally. The emphasis has now shifted toward a model in which research examines the psychological sequelae and antecedents that affect a woman who seeks an abortion. In examining past research that covers a variety of legal climates, one must differentiate between research on "therapeutic" abortion, which requires medical or psychiatric consultation in the decision-making process, and research on open abortion, in which the woman involved is the sole decision maker. A recent review by Adler et al. (7), which limited itself to U.S. studies in order to reduce the confounding variables of social, cultural, and legal differences, found that "legal abortion of an unwanted pregnancy in the first trimester does not pose a psychological hazard for women" in the legal context of open abortion. None of the reviews mentioned there, however, address the issue of denied abortion.

Although many studies have examined the short-term consequences of therapeutic abortion, few have used either a comparison group or objective measure of symptoms. A few studies of open abortion do meet these criteria. Freeman et al. (8), in one of the more objective studies involving over 400 women, found that SCL-90 scores were elevated on several subscales in women before the procedure but decreased significantly toward normal quite rapidly after the abortion. Those scales on which the preabortion scores were highest, indicating the highest level of distress, had the greatest decrease after the abortion. In 1985 Major et al. (9) surveyed over 200 women before their abortion, 30 minutes afterward, and at the end of 3 weeks, using the Beck Depression Inventory and clinical interviews. They found the average score to be in the nondepressed range immediately after the abortion; 3 weeks after the abortion the women's mood had continued to improve, and there was less depression and less anticipation of negative consequences. Using the SCL-90 before and immediately after the procedure, Cohen and Roth (10) demonstrated a significant drop after the abortion in scores on the depression subscale, with similar drops in scores on the anxiety subscale of the SCL-90 and the Impact of Events Scale. Prospectively following hospital admissions in a study of therapeutic abortion in the United Kingdom, Brewer (11) found an admission rate of 0.3/1,000 for postabortion psychosis compared to a rate of 1.7/1,000 for postpartum psychosis in normal-term deliveries.

Other studies, using less objective measures and examining therapeutic abortions that required psychiatric or other medical consultation, still seem to point in the same direction when comparison groups are available. Ewing and Rouse (12) found depressive symptoms in 3% of women granted abortions for psychological indications and in 12% of those women with previous psychiatric contact. Mackenzie (13) commented that women were more likely to be depressed before the abortion than after and that 78% expressed predominant feelings of relief, while 33% reported some feelings of guilt, with 80% of the guilt rated as mild. Niswander and Patterson (14) found that most women report an improvement in emotional health. In their study, women who had abortions for medical reasons reported more "unfavourable reactions" than those who had abortions for psychogenic indications. In 1965 Jansson (15) reported the following rates of admission to psychiatric hospitals immediately after abortion or delivery: 0.70% after term delivery, 1.92% after legal abortion, and 0.27% after illegal abortion and spontaneous abortion. It was felt that the apparent difference in reaction to legal and illegal abortion was due to the much higher proportion of women in the legal abortion group (over 50%) with a previous psychiatric history. Unmarried women were also more likely to be hospitalized. Other short-term studies that lack such comparison groups are summarized in table 1 (3, 16–27).

When studies have examined the effects of abortion months or years after the procedure, similar trends continue. Brody et al. (28) and Niswander et al. (29), who used pregnant women with normal deliveries for control subjects in examining therapeutic abortion, showed that MMPI scores, which may be abnormal

**TABLE 1. Studies of the Immediate Psychological Sequelae of Abortion**

| Study and Year | Number of Subjects | Results | |
|---|---|---|---|
| | | Positive | Negative |
| Ekblad, 1955 (16) | 479 | — | 2% had severe self-reproach |
| Simon and Senturia, 1966 (3) | —[a] | — | 0%–41% felt guilty |
| Patt et al., 1969 (17) | 35 | — | 40% had symptoms, all mild; in one-half, symptoms were present before abortion |
| Bacon, 1969 (18) | 9 | 55% felt considerable relief | 33% felt mild guilt lasting a few days |
| Walter, 1970 (19) | —[a] | — | 0%–30% felt mild guilt |
| Osofsky and Osofsky, 1972 (20)[b] | 250 | 65% were happy | 14% were sad, 24% felt guilty |
| Lazarus, 1985 (21)[b] | 292 | 76% felt relief | 15% felt guilty and were depressed; 10% had overall negative symptoms |
| Pare and Raven, 1970 (22) | 128 | Most experienced marked relief and improved relationships | A few felt mild guilt for 1–2 weeks |
| Marder, 1970 (23) | 147 | Most experienced marked relief of symptoms and improved relationships | — |
| Bracken et al., 1974 (24) | 489 | Positive reactions increased with more support | — |
| Adler, 1975 (25)[b] | 95 | Most had positive feelings | A few felt guilt and doubt |
| Spaulding and Cavenor, 1978 (26)[b] | 2[c] | — | Two subjects developed psychosis, one organic |
| McAll and Wilson, 1987 (27)[b] | 6[c] | — | Six subjects developed psychiatric symptoms |

[a] Review study.

[b] Studies examined abortion on request. All other studies involved therapeutic abortion requiring some degree of psychiatric or other medical consultation.

[c] Case reports.

before the abortion, normalize within 6 months to a year after the abortion. The control subjects, who had less abnormal scores before delivery, showed no change in their scores after delivery. In the study by Brody et al., a group of women who were denied abortion continued to have quite abnormal scores after the delivery of the infant.

Studies of open abortion show similar results. Athanasiou et al. (30), who also used pregnant women with normal deliveries as control subjects and matched for socioeconomic status, found no difference in MMPI and SCL-90 scores between the two groups after delivery or abortion. A study by Jacobs et al. (31), who used women undergoing minor gynecologic surgery as control subjects, showed higher preabortion scores for the pregnant women on the Psychopathic Deviate, Schizophrenia, Hysteria, and Depression scales of the MMPI; these differences disappeared after the abortion. Using a different control group, Zabin et al. (32) examined a group of adolescents who presented initially for pregnancy testing and subsequently studied three groups—those who were pregnant and chose to abort the fetus, those who were pregnant and chose to complete the pregnancy, and those whose test results were negative. One and 2 years later they found that the abortion group showed no evidence of psychological distress compared to either control group and that, indeed, there was a nonsignificant trend toward better psychological health with less anxiety on the State-Trait Anxiety Inventory and more internal locus of control. In addition, the women who completed their pregnancy showed a significant economic deterioration afterward and were significantly more likely to discontinue school than the abortion group; this difference actually increased between the first and second years after delivery or abortion. In a study in Denmark (33) that tracked psychiatric hospitalization rates for 3 months after abortion or delivery, there was no difference between postpartum and postabortion rates in married and never married women. Higher postabortion rates of admission were found in separated, divorced, and widowed women, women who were more likely to be isolated and alone.

Among the older studies of therapeutic abortions with less rigorous methodology, Peck and Marcus (34) and Smith (35) found more symptoms of depression and negative feelings, up to 2 years afterward, in women for whom the abortion was performed for medical/genetic indications. Significant distress occurred in less than 10% of women who had abortion for psychosocial indications. Ewing and Rouse (12) found that approximately 95% of their study subjects reported improved emotional health as a result of the abortion at 2-year follow-up.

Table 2 presents data on other long-term studies (16, 17, 22, 36–47) that lacked comparison or control groups (thereby making interpretation difficult). All studies in this group involved therapeutic abortion in which psychiatric or other medical consultation was required before the abortion. Noteworthy, again, is the relative lack of significant negative responses in the women. The two studies that found relatively higher rates of negative responses are those of Wallerstein et al. (42) and Ashton (46). The low response rate (less

**TABLE 2. Studies of the Long-Term Psychological Effects of Abortion**[a]

| Study and Year | Length of Follow-Up | Number of Subjects | Results | |
|---|---|---|---|---|
| | | | Positive | Negative |
| Ekblad, 1955 (16) | 2 years | 479 | — | 11% had self-reproach |
| Kretzschmar and Norris, 1967 (36) | 1–5 years | 24 | — | — |
| Patt et al., 1969 (17) | 2–6 months | 35 | 74% | 14% |
| Pare and Raven, 1970 (22) | 3 months | 321 | — | 13% felt guilty |
| Whittington, 1970 (37) | 2–12 months | 31 | 87% | 6% |
| Ford et al., 1971 (38) | 6 months | 22 | — | 14%[b] |
| Margolis et al., 1971 (39) | 3–6 months | 43 | 67% | 9% |
| Meyerowitz et al., 1971 (40) | 1–84 months | 114 | 78% | 9% |
| Todd, 1972 (41) | 1–3 years | 83 | 91% had no adverse symptoms | — |
| Wallerstein et al., 1972 (42) | 5–7 months | 22 | — | 32% |
| Perez-Reyes and Falk, 1973 (43) | 3 months | 41 | 75%–90% | — |
| Lask, 1975 (44) | 3 months | 50 | 68%–89% | 8% |
| Greer et al., 1976 (45) | 18 months | 217 | — | 7% felt guilty, 19% had other symptoms |
| Ashton, 1980 (46) | 6 weeks | 64 | — | 24% felt guilty, 31% felt worried |
| Schmidt, 1981 (47) | 3–6 years | 10 | Normalization of scale scores[c] | — |

[a] All studies involved therapeutic abortion requiring some degree of psychiatric or other medical consultation.

[b] According to the MMPI.

[c] On the Hostility and Direction of Hostility Questionnaire and the Symptom-Sign Inventory.

than 20%) to a mailed questionnaire in the first study and the minor nature of symptoms measured in the second may account for the difference.

Table 3 presents data on studies (12, 14, 17, 22, 36, 37, 39, 44, 45, 48) that queried subjects concerning the presence of regrets after the procedure (a measure of ambivalence about the abortion decision). This question is frequently posed, and yet despite the subjective nature of the question, the results are surprisingly uniform. They reveal that for the large majority of women, the decision about abortion, although undoubtedly difficult, is not one for which a great deal of conscious ambivalence exists.

In women undergoing induced abortion, several factors have been identified that correlate with higher rates of psychological distress after abortion. As previously mentioned, it has been clearly demonstrated that a medical or genetic indication for abortion increases the risk of a negative reaction (5, 6, 34, 35). Previous psychiatric contact has also been clearly shown to increase the likelihood of the woman having a negative emotional response to the abortion (12, 34, 38). The presence of support seems to be a more complex issue, with possibly contradictory results. Several studies have shown that a woman's perceived degree of support at the time of the abortion was positively correlated with a good psychological response afterward (20, 24, 33, 49, 50), but Major et al. (9) found that women whose partners accompanied them to the clinic for the procedure were more likely to feel depressed afterward and experienced more physical complaints. Similarly, Robbins (51) found that single women who maintained a strong relationship with their partners after the abortion were more likely to experience regrets at 1 year and had more negative scores on the MMPI at 6 months.

**TABLE 3. Studies of the Prevalence of Regrets After Abortion**[a]

| Study and Year | Total Subjects | Subjects With Regrets |
|---|---|---|
| Greer et al., 1976 (45) | 217 | 3% at 3 months, 3.7% at 18 months |
| Niswander and Patterson, 1967 (14) | 116 | 3% |
| McCoy, 1968 (48) | 62 | 32% had regrets of some degree at some time |
| Ewing and Rouse, 1973 (12) | 126 | 3% |
| Margolis et al., 1971 (39) | 43 | 4.4% |
| Patt et al., 1969 (17) | 35 | 5.7% |
| Whittington, 1970 (37) | 31 | 6.5% |
| Kretzschmar and Norris, 1967 (36) | 24 | 12.5% had occasional regrets |
| Lask, 1975 (44) | 50 | 16% had some regrets |
| Pare and Raven, 1970 (22) | 321 | 1.6% |

[a] All studies involved therapeutic abortion requiring some degree of psychiatric or other medical consultation.

The decision on whether to abort the fetus or to carry it to term is a complex one that has several effects on the psychological state of the woman. Not surprisingly, women undergoing mid-trimester abortions experienced more difficulty with the decision than those having first-trimester abortions (25), and they experienced greater ambivalence about the pregnancy (52). They also appeared more likely to experience negative reactions after the abortion (25, 30, 53), particularly if the late abortion required induction of labor and delivery (54). Adolescents who felt that they themselves made the decision to abort, regardless of the length of the pregnancy, without pressure from parents or oth-

**TABLE 4. Studies of the Outcome of Pregnancy After Abortion Was Denied**

| Study and Year | Number of Subjects | Full-Term Pregnancy (%) | Abortion (%) | |
|---|---|---|---|---|
| | | | Induced | Spontaneous |
| Lindberg, 1948 (57) | 344 | — | 14.5 | — |
| Delcomyn, 1952 (58) | 136 | — | 39 | — |
| Hultgren, 1959 (59) | 4,214 | 85.6 | 10 | 4.4 |
| Hook, 1963 (60) | 249 | 69 | — | — |
| Peck and Marcus, 1966 (34) | 9 | — | 56 | — |
| Forssman and Thuwe, 1966 (61) | 196 | 65.3 | 34.7 | — |
| Pare and Raven, 1970 (22) | 120 | — | 36 | — |
| Meyerowitz et al., 1971 (40) | 4 | — | 75 | — |
| Hultin and Ottosson, 1971 (62) | 1,008 | 81.2 | — | — |
| Dytrych et al., 1975 (63) | 439 | 72 | 10 | 18 |
| Hunton, 1977 (64) | 253 | 34.5 | 46.6 | 5 |
| Drower and Nash, 1978 (65, 66) | 69 | 55 | — | — |
| Binkin et al., 1983 (67) | 258 | 72 | 20 | — |

**TABLE 5. Studies of the Adoption of Children Born After Abortion Was Denied**

| Study and Year | Number of Children Born | Children Adopted Away (%) |
|---|---|---|
| Malmfors, 1951 (68) | 85 | 8 |
| Aren and Amark, 1957 (69) | 162 | 7.4 |
| Forssman and Thuwe, 1966 (61) | 120 | 6.7 |
| Hook, 1963 (60) | 204 | 7.4 |
| Pare and Raven, 1970 (22) | 73 | 19 |
| Drower and Nash, 1978 (65, 66) | 38 | 16 |

ers, were less likely to experience negative emotions after the abortion (24, 43).

Several studies have examined the effect of the woman's preabortion psychological status on her postabortion course. Spreckhard (55), in looking at women who reported significant postabortion distress, found that they used a great deal of denial and repression, as well as projection onto their partner or the medical staff, in dealing with the stress of their pregnancy and subsequent abortion. These women also described high degrees of boundary ambiguity with respect to the aborted fetus and maintained an ongoing, high level of attachment to the fetus, despite its loss. Athanasiou et al. (30) found that women who experienced the most distress after an abortion were more likely to have lower self-esteem, a higher sense of alienation, and less knowledge of contraceptives before the abortion. Bracken et al. (56) found that women with a relatively internal locus of control and high level of ego resiliency responded most favorably to the abortion.

## PSYCHOLOGICAL SEQUELAE OF DENIED ABORTION

Even more difficult to determine, and hence even less often examined, is the issue of the effects of denying abortion on the mother and child. The studies that have been done are often older, since the access to abortion has improved in many countries.

Before an examination of the direct effects of the denied abortion, two issues need to be clarified. How many pregnancies will go on to completion if abortion is not performed as requested, and of those, how many women will eventually put their infants up for adoption? Table 4 presents data on studies (22, 34, 40, 57–67) that addressed the first question. Particularly in the more recent studies, a large proportion of women (over 40% in one large study [64]) will continue to seek abortion elsewhere and will succeed. Particularly alarming are the reported rates of "spontaneous" abortion in this population. Because women who request abortion are often past the first trimester (the stage at high risk for spontaneous abortion), truly spontaneous miscarriage should be rare. However, when these pregnancies are carried to term, studies (22, 60, 61, 65, 66, 68, 69) show that the proportion of children put up for adoption is quite small, ranging from 6.7% to 19.0% (table 5). From these studies it would seem that when an abortion request is denied, the result is often either an abortion obtained elsewhere or a mother raising an infant from an unwanted pregnancy in the situation that led her to request the abortion in the first place.

The few studies that have examined the effect of the denied abortion on the parents have focused on the effects on the mother. While the effects on the father have been reported occasionally in an anecdotal fashion, systematic studies are lacking. The earliest study (60) evaluated 249 women 7 years after the denied abortion. It found that 27% of the women had been able to cope fully with the pregnancy and the child, 22% still showed signs of mental illness and poor adjustment, and 51% had shown symptoms of mental disturbance and great emotional strain for a period of considerable length since the birth but seemed to have overcome these problems. Unfortunately, the study did not distinguish between women who aborted the fetus elsewhere, gave the child up for adoption, or raised the child themselves. Drower and Nash (65, 66) reported that those women denied abortion expressed greater guilt and anxiety than women for whom an abortion had been performed. In the most compelling of these studies, Pare and Raven (22) looked at 73 women 1–3 years after their request for abortion was denied and found that 59% reported that they accepted the child and were glad that they had not aborted the fetus, while 34% reported that the child was a burden that they frequently resented. Admittedly quite subjective, these studies nonetheless show that although an unwanted pregnancy does not always result in an unwanted child, there is reason to be concerned that significant numbers of these women will continue to harbor quite negative feelings toward their children, feelings that are easily elicited by interviewers.

The final and most difficult question concerns the effects on the children themselves of being born after an abortion request is denied. In a study of the world literature on infanticide, Resnick (70) found that 83% of the newborns killed and 11% of the children killed by their mothers had been born of unwanted pregnancies. Studies by Blomberg (71) and Hultin and Ottosson (62) found no difference in the rate of pregnancy-related or perinatal complications in children born of unplanned pregnancies, while Nielsen (72) found a slightly above normal rate of physical abnormalities in newborns born in this situation.

In a classic study that continues to have relevance today, Forssman and Thuwe (61) compared, up to age 21 years, 120 children born of unwanted pregnancies with control subjects matched by date of birth. They found that the study group had a more insecure childhood, more psychiatric care, more childhood delinquency, and more early marriages and were more often young mothers; all of these findings were statistically significant. Even after socioeconomic class was controlled, fewer of the study subjects had more than secondary education and fewer were without defects of any kind, when all these problems were grouped together. A recent update (73) on the study group, then 35 years old, found that the differences were diminishing; however, the study subjects were still significantly more likely to appear on some kind of registry, indicating contact for psychiatric care, because of crime or delinquency, or for public assistance. Hook (cited in reference 74) studied 88 children born after abortion was denied, comparing them with a control group made up of the same-sex classmate of nearest age to each study individual. At age 18, the boys in the study group had a higher rate of conduct disorder, criminality, and unstable homes, with lower emotional maturity. At 23, more of the men in the study group were likely to require economic assistance, and the women in the study group began to show evidence of lower self-esteem and more depression. A study (75) with a more rigorous control group, which was matched for age, sex, number of siblings, and socioeconomic class at the time of the child's birth, evaluated the children until their 15th birthday. The study group had poorer school performance throughout this time, as well as more neurotic and psychosomatic symptoms recorded in the school health registry, and more likelihood of being registered with social welfare authorities.

Perhaps the most ambitious study to date is that of Matejcek et al. (63, 76–80), who compared a control group and a group of 220 children born in Prague in 1961–1963, after abortion was denied. The two groups were matched for socioeconomic class, sex, age, birth order, number of siblings, and parental marital status. Early findings in 1970 found that the study subjects were less likely to be breast fed, had more acute medical illness, were more likely to be reported as difficult when they were preschoolers, were more likely to be rejected by friends and teachers, had poorer school performance, and were less adaptive to frustration; boys were more likely to be affected. At ages 14–16 (79), 216 of the original 220 were still being studied. School performance in the study group continued to deteriorate, and various indicator scales showed that this group had more negative relationships with their mothers. Current studies (80) of the children in their early 20s show an ongoing propensity for social problems that remains markedly prevalent in this group. The study subjects had more job dissatisfaction and fewer friends and reported dissatisfaction with life (all significant findings) and less education, more criminality, and more registration by the authorities for drug and alcohol problems (trends).

## DISCUSSION

In spite of the numerous difficulties facing researchers who attempt to address the issue of therapeutic abortion, the findings do appear to be remarkably uniform. Precise answers, unaffected by bias, are probably not possible, but the research examined here does highlight several things.

Immediately after abortion, symptoms of distress and dysphoria do occur in many women. However, these symptoms seem to be continuations of symptoms present before the abortion and more a result of the circumstances leading to the abortion than a result of the procedure itself. Indeed, many studies report significant positive feelings after the abortion. When the women are studied over the course of the episode, the dysphoria is found to be on the wane after the abortion. Longer-term studies, over months and years, show similar trends; the majority of women express positive reactions to the abortion, and only a small minority express any degree of regrets. Similarly, negative feelings present before the abortion disappear, with normalization of various scores.

Although it is difficult to generalize about factors that are more likely to be involved in women who experience a negative psychological response to abortion, and potentially misleading when dealing with an individual, several trends are evident. Abortion for medical or genetic indications, a history of psychiatric contact before the abortion, and mid-trimester abortions often result in more distress afterward. When women experience significant ambivalence about the decision or when the decision is not freely made, the results are also more likely to be negative. The issue of support is a more complex one and is not easily measured; many studies indicate that support by the parent or partner can be positive, although apparently contradictory studies exist. Prior psychological coping styles and resiliency also appear to play an important role in the psychological sequelae of an abortion, in that certain defensive styles such as projection, repression, and denial may hinder a woman's working through and resolving the loss of a fetus, particularly when it is one that is ambivalently regarded.

When abortion is denied, a different picture seems to arise. Many women, up to 40% in some studies, have the abortions elsewhere, depending on availability. Relatively few of the children are put up for adoption, and the majority born of unwanted pregnancies are raised by their biological mother. A significant minority—about 30%—of the women examined in the few long-term studies continue to report negative feelings toward their child and difficulty adjusting.

Finally, the most disturbing part of the whole issue is the evidence of significant negative effect on the child. With the caveat that the unwanted pregnancy does not necessarily result in an unwanted child, the carefully designed and executed prospective studies of Matejcek et al., Hook, Blomberg, and Forssman and Thuwe reveal long-lasting, broadly based, negative effects of the denial of abortion on the children subsequently raised in the situation that the parents had tried so desperately to avoid.

While this paper has not addressed any of the ethical issues raised by therapeutic abortion, it has attempted to give a psychiatric perspective that has hitherto been unavailable in this debate. Further research on some of the questions examined is important, particularly if society moves toward more restrictive legislation on this issue, since the question of the effects on the mother and the child in particular has only begun to be explored.

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# Suicide and Guilt as Manifestations of PTSD in Vietnam Combat Veterans

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*Objective: Although studies have suggested a disproportionate rate of suicide among war veterans, particularly those with postservice psychiatric illness, there has been little systematic examination of the underlying reasons. This study aimed to identify factors predictive of suicide among Vietnam combat veterans with posttraumatic stress disorder (PTSD). Method: Of 187 veterans referred to the study through a Veterans Administration hospital, 100 were confirmed by means of a structured questionnaire and five clinical interviews as having had combat experience in Vietnam and as meeting the* DSM-III *criteria for PTSD. The analysis is based on these 100 cases. Results: Nineteen of the 100 veterans had made a postservice suicide attempt, and 15 more had been preoccupied with suicide since the war. Five factors were significantly related to suicide attempts: guilt about combat actions, survivor guilt, depression, anxiety, and severe PTSD. Logistic regression analysis showed that combat guilt was the most significant predictor of both suicide attempts and preoccupation with suicide. For a significant percentage of the suicidal veterans, such disturbing combat behavior as the killing of women and children took place while they were feeling emotionally out of control because of fear or rage. Conclusions: In this study, PTSD among Vietnam combat veterans emerged as a psychiatric disorder with considerable risk for suicide, and intensive combat-related guilt was found to be the most significant explanatory factor. These findings point to the need for greater clinical attention to the role of guilt in the evaluation and treatment of suicidal veterans with PTSD.*

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Since the turn of the century, when Durkheim first reported suicide rates among European military men that were up to 10 times those among male civilians of comparable age (1), the link between military service and suicide has been of clinical interest. However, it was not until after World War II that systematic analyses were undertaken which pointed to a higher rate of suicide among men who had served in the military than among other men of the same age (2–5). Suicidal behavior was observed to be particularly frequent among veterans with combat experience (4) and postmilitary psychiatric illness (2, 6).

Since the war in Vietnam, there have been numerous reports of a disproportionate rate of suicide among veterans of that war (7–14). Using a wide diversity of methods, measures, and sample selection criteria, these studies provided estimates of the rate of suicide among Vietnam veterans that ranged between 11% (12) and 65% (13) higher than the rate for nonveterans of the same age.

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Although a recent epidemiological analysis suggested that the total number of Vietnam veterans who have committed suicide has probably been overestimated (15), the accumulated evidence of the past two decades points to suicidal behavior among veterans as part of the complex legacy of the Vietnam experience. To date, however, there has been little systematic examination of the underlying reasons for this phenomenon.

In view of the findings of the World War II studies (2–6), we suspect that the suicide rate for Vietnam veterans would be much higher if the figures were restricted to combat veterans and that it would be higher still if they included only veterans with diagnoses of posttraumatic stress disorder (PTSD). Although national suicide statistics for these different groups of veterans do not exist, clinicians who have worked closely with men who saw considerable combat in Vietnam have noted that suicidal behavior is frequently a manifestation of PTSD (16–19).

This article aims to provide insight into some of the factors associated with suicide among Vietnam combat veterans with PTSD. It focuses in particular on lingering guilt related to wartime actions or events. It is based on data collected as part of a 5-year research and treatment project at a Veterans Administration (VA) hospital.

## METHOD

Over the 5-year period, 187 male Vietnam veterans were referred to the project on the basis of two selection criteria: combat experience in Vietnam and suspected PTSD. The primary sources of referral were clinicians in the hospital's inpatient and outpatient units, staff at local Vietnam Veteran Outreach Centers, and individual veterans who were familiar with our work. All 187 men referred were initially included in the project, and 122 completed a comprehensive evaluation procedure, which we have described elsewhere in detail (20).

At the beginning of the procedure, each veteran completed a 46-page questionnaire that included (in addition to items dealing with his life before, during, and after his service in Vietnam) the Revised Combat Scale (21) and a checklist of PTSD symptoms based on the *DSM-III* diagnostic criteria for the disorder. He then participated in a series of five semistructured interviews that elaborated key wartime experiences and systematically reviewed all current and lifetime PTSD symptoms. Each symptom experienced by the veteran was explored for specific form and content, frequency and severity, and relation to actual wartime experiences.

Finally, the interviews elicited additional detailed information about the individual's life before and after his service in Vietnam. Of particular interest was the issue of suicidal behavior during these periods, including both suicide attempts and suicidal preoccupation or ideation.

Of the 122 veterans who completed the evaluation procedure, exactly 100 were confirmed both as having had combat experience in Vietnam and as meeting the full *DSM-III* criteria for a current diagnosis of PTSD. All 100 veterans also met the *DSM-III-R* criteria for the disorder. The present analysis is based on these 100 cases. Sixty veterans were inpatients at a VA hospital at the time of their participation in the study and had been admitted for symptoms associated with PTSD, including drug or alcohol abuse. The remaining 40 veterans were treated on an outpatient basis.

These veterans were being treated an average of 15 years following their service in Vietnam. As in the general population of men who fought in Vietnam, their average age at the time of their war experience was just under 20 years. According to their scores on the Revised Combat Scale, these veterans had had considerably heavier combat exposure than the general population of those who served in Vietnam (21). Seventy percent of this group, compared to 27% of all Vietnam veterans, fell into the "heavy combat" classification, with scores of 10 or more on the 14-point scale. Only one of our veterans, compared to 35% of all Vietnam veterans, received a score of less than 4, the minimum for a designation of "moderate combat."

Following a procedure developed by us for the integration of structured and psychodynamic interview material (22, 23), the questionnaire and interview data obtained from the veterans were coded according to 118 preservice, service, and postservice variables. Using a closed-ended instrument, two members of the research team independently coded each case for all 118 variables. In each case one of the coders had firsthand knowledge of the veteran through having conducted the evaluation interviews and/or having treated him in follow-up psychotherapy. Interrater reliability on initial coding of the instrument was high, with a coefficient of reliability (24) of 0.88. All inconsistent ratings were reviewed by a third coder, and resolution was reached through discussion of the entire case, including review of the questionnaire and interview transcripts.

All variables included in the coding instrument were measured in categorical form, and most were dichotomized for the final analysis. Chi-square tests with Yates' correction were used to assess the significance of the relationships among these variables; suicide attempts and preoccupation with suicide were treated as the key dependent variables. Logistic regression analyses were performed to assess the relative contributions of the significant independent variables in predicting suicidal behavior among the veterans studied. All analyses were made with the SPSS statistical package (25). A p value of 0.05 or less was generally considered to indicate a significant difference. This was adjusted, however, by using the Bonferroni correction, when multiple tests were performed on the same set of data.

## RESULTS

Nineteen of the 100 combat veterans given current diagnoses of PTSD had attempted suicide at least once since returning from Vietnam. Fifteen more had been preoccupied with suicide for a considerable part of their lives since they left the service. According to the commonly accepted clinical definition, this involved having "seriously thought about, planned or wished to commit suicide" (26). The seriousness of the suicidal intent among these veterans is suggested by the fact that during the course of study, three of the men who were diagnosed as suicidal actually did kill themselves.

The 66 veterans who had neither attempted nor been preoccupied with suicide were considered nonsuicidal. Comparisons between the suicidal and the nonsuicidal veterans showed similar frequency distributions of almost all PTSD symptoms. However, certain highly significant differences centering most strikingly on the issue of guilt were revealed.

Among all the variables examined, we found that the presence of persistent guilt related to wartime experiences provided the sharpest contrast between the suicide attempters and the nonsuicidal veterans. Two distinct kinds of guilt played a significant role in determining the vulnerability to suicide among these veterans with PTSD: guilt about combat actions and guilt about surviving when others had died. Although both combat guilt and survivor guilt were found among a high percentage of all the veterans with PTSD (63% and 46%, respectively), there were significant differences in the frequencies of these symptoms between the suicide attempters and the nonsuicidal veterans.

Guilt related to combat actions was marked in all 19 of the suicide attempters but in only 48.5% (N=32) of the 66 nonsuicidal veterans ($\chi^2=14.24$, df=1, $p<0.001$). Similarly, marked survivor guilt was present in a high proportion of the veterans who had attempted suicide (73.7%, N=14), compared to 36.4% (N=24) of those who were nonsuicidal ($\chi^2=6.87$, df=1, $p=0.009$).

The suicide attempters with PTSD could be distinguished from the nonsuicidal veterans with PTSD by a number of postservice symptoms besides guilt. All 19 veterans in the former group evidenced anxiety as an associated symptom of the disorder, in contrast to 66.7% (N=44) of the 66 nonsuicidal veterans ($\chi^2=6.90$, df=1, $p=0.009$). Almost as many of the suicide attempters (94.7%, N=18) showed marked depression as an associated symptom, compared to 56.1% (N=37) of the nonsuicidal group ($\chi^2=8.04$, df=1, $p=0.005$). A significantly larger proportion of the suicide attempters (89.5%, N=17) than of the nonsuicidal veterans (53.0%, N=35) also had severe cases of PTSD ($\chi^2=6.79$, df=1, $p=0.009$). Even when we used the Bonferroni correction to adjust the 0.05 level of significance to 0.01 (0.05/5=0.01) to account for the fact that the five separate chi-square tests were done on the same data, each of these findings remained statistically significant.

To assess the relative contributions of these variables in predicting suicide attempts, a forward stepwise logistic regression analysis was performed. Of the five independent variables included in the analysis (guilt about combat actions, survivor guilt, anxiety, depression, and severity of PTSD), only two added significantly to the predictive model. The first variable selected, guilt about combat behavior, yielded a model chi-square value of 22.98 (df=1, $p<0.001$), indicating that this variable made a highly significant improvement over the constant in predicting suicide attempts in this group of subjects. When we entered the second variable, depression, into the regression model, the model chi-square increased to 27.60 (df=2, $p<0.001$). The improvement chi-square value associated with depression was also significant ($\chi^2=4.62$, df=1, $p=0.03$).

In this final model, the goodness-of-fit chi-square value of 51.00 (df=82, $p=0.997$) had an exceptionally high probability of occurrence. Thus, a regression model that predicts suicide attempts among veterans with PTSD on the basis of combat guilt and depression very closely matches the "perfect" predictive model. The logistic regression coefficients (betas) for these two variables (9.16 and 1.95, respectively) indicate the relative contributions of each to the model and point in particular to the importance of combat guilt in predicting suicide attempts among the veterans studied.

The characteristics that distinguished the veterans who had made suicide attempts from the nonsuicidal group were found as well among a considerable, although not statistically significant, number of the 15 veterans who were preoccupied with suicidal thoughts. This was particularly true of guilt about combat actions, which we found among 80% (N=12) of those with suicidal ideation, and only 48.5% (N=32) of the nonsuicidal veterans ($\chi^2=3.71$, df=1, $p=0.05$).

When a logistic regression analysis was performed using the same set of five independent variables as were tested in relation to suicide attempts, guilt about combat emerged as a statistically significant predictor of preoccupation with suicide. With this one variable, which had a beta coefficient of 1.45, the regression model yielded a significant chi-square value of 5.24 (df=1, $p=0.02$). Further, the nonsignificant goodness-of-fit chi-square value ($\chi^2=81.00$, df=1, $p=0.42$) indicated that when only the variable of combat guilt is used, this predictive model for suicidal preoccupation does not significantly differ from the "perfect" model.

Since guilt about combat actions was so significant in predicting both suicide attempts and preoccupation with suicide, the combat experiences of the suicidal veterans were examined for possible determinants of their lingering guilt. We looked at specific combat actions that might be considered to have produced the guilt later experienced by the suicidal veterans, i.e., inadvertent or deliberate killing of civilians, mutilation or torture of the enemy, wounding or killing other Americans, rape, and passively witnessing nonmilitary actions by fellow soldiers. Somewhat unexpectedly, such combat behavior was sufficiently frequent in the histories of the nonsuicidal as well as the suicidal veterans that it did not serve to distinguish the two groups. For example, the most frequent such action, the killing of civilians, which was found among 68.4% (N=13) of the 19 suicide attempters, was found among an only slightly smaller proportion of the 66 nonsuicidal veterans (57.6%, N=38). In the majority of cases in both groups, women and children were among those killed, which was particularly disturbing to the veterans.

Although the overt combat behavior of the suicidal and nonsuicidal veterans was quite similar, further analysis revealed significant differences between the two groups in the affective states under which the nonmilitary killing of civilians occurred. Sixteen (84.2%) of the 19 suicide attempters had felt out of control as a result of excessive fear or rage during considerable periods of their tours of duty in Vietnam, including the situations in which their actions led to deaths about which they felt guilty. Among the 13 suicide attempters who had killed civilians, for example, 12, or 92.3%, had felt out of control when they did so. Only 17 (42.5%) of 40 nonsuicidal veterans who had killed civilians had done so while feeling out of control ($\chi^2$=9.84, df=1, p=0.002).

Although preservice variables were useful in understanding individual cases, none was found to be significantly related to postservice suicidal behavior. None of the veterans we studied had made a suicide attempt or showed evidence of preoccupation with suicide prior to his combat experience, nor was loss of control a significant factor in the precombat histories of either the group that became suicidal or the group that did not.

## DISCUSSION

The most significant finding of our analysis was the clear and consistent relationship between veterans' combat-related guilt and postservice suicidal behavior. Combat-related guilt, usually related to having killed prisoners of war, was identified as an important factor in the stress disorders of American veterans studied several years after their combat experiences in World War II (27), although the linkage between guilt and suicide has not been previously described.

The nature of guerrilla combat in Vietnam, the uncertainty about who was the enemy, the emphasis on body counts, and the use of women, children, and the elderly as combatants undoubtedly contributed to combat actions about which veterans felt guilty. Our analysis showed, however, that the affective state in which the veteran had acted during combat was more significant in determining postservice guilt than was the action itself. A veteran who had killed civilians through firing under orders on a village labeled as unfriendly, and who in time came to question the judgment of his superiors and his own role in following their orders, was not as likely to feel marked guilt or become suicidal about his behavior as a veteran whose killing of civilians had occurred while he was feeling out of control because of terror or rage.

Survivor guilt was also shown to be significantly related to postservice suicide attempts but not to suicidal preoccupation. Although survivor guilt has been described as an almost omnipresent symptom in the traumatic stress disorders of concentration camp survivors (28–30) and survivors of the atomic explosion at Hiroshima (31), among our Vietnam veterans we did not find survivor guilt to be as frequent as guilt about combat actions. Most probably this is because virtually all survivors of the concentration camps and Hiroshima lost someone close to them, whereas not all of our Vietnam veterans lost close friends in combat. Among the 72 who did, 52.8% (N=38) had marked survivor guilt, compared to only 28.6% (N=8) of the 28 veterans who did not lose close friends ($\chi^2$=4.76, df=1, p=0.03).

The logistic regression analysis did not identify survivor guilt as a significant predictor of suicide attempts, suggesting that its effect overlaps to a considerable degree with that of guilt concerning combat actions. Additional one-way analyses provided some evidence of the importance of the concurrent presence of the two types of guilt. Forty of the 100 veterans studied, for example, showed both marked guilt about combat actions and marked survivor guilt. Among this group 14, or 35.0%, had made a suicide attempt. In contrast, none of the 30 veterans who showed neither marked combat guilt nor survival guilt had attempted suicide ($\chi^2$=13.13, df=1, p<0.001).

Moreover, among the 17 veterans who had killed civilians while feeling out of control and felt guilty about such actions but were not suicidal, only two had marked survivor guilt. By contrast, nine of the 12 suicide attempters who had killed civilians while feeling out of control experienced marked survivor guilt in addition to guilt concerning their combat actions ($\chi^2$=12.21, df=1, p<0.001). These findings suggest that the combination of these two types of guilt plays a role in determining suicide risk among veterans.

For most of the suicidal veterans, the clinical data obtained through the interviews elaborated the linkages between combat incidents about which a veteran felt guilty and the loss that led to survivor guilt. Sometimes the loss of a combat buddy came first and contributed to a state of rage which, in turn, led to a loss of control over combat behavior. In other cases, the loss of control as a result of extreme fear led to actions about which the individual felt guilty, which was reenforced when a friend was killed. In either case, the veteran was apt to feel that a friend who did not deserve to die had died, while he himself, who did not deserve to live, was alive.

In most of the suicidal cases, the actions that had been committed were of a nature that made the postservice guilt and nightmares of punishment seem understandable and almost inevitable. A typical experience was that of a forward artillery spotter who, after seeing friends killed in combat, called for artillery fire on a village he knew to be friendly. Through his binoculars he saw an old woman with betel nut stains on her teeth who was blown up by a shell while she was running toward the fire as if trying to stop it. At the time, he was laughing, but subsequently he could not believe he had become so callous. In his most repetitive postservice nightmare, he is captured, tied to a pole, and spat on by the villagers, led by the old woman with the stained teeth.

In a few cases, the combat actions were not as unequivocal, and the particular meaning given to them by the veteran was integral to an understanding of his postservice suicidal behavior. One man, for example, shot and killed a woman who was advancing toward his patrol and did not heed his order to stop. She turned out to be wired with explosives, but the veteran ruminated about whether he could have stopped her by firing a warning shot or wounding her in the legs. Subsequently, his closest friend, who had extended his tour in Vietnam so that they could come home together, was killed. The veteran linked his guilt about both deaths with the guilt and rage he felt toward his mother, who had abandoned him as a child. In his recurrent dreams of the Vietnamese woman, her image would merge with that of his mother.

The suicidal veterans varied considerably in the degree to which they were in touch with their combat-related guilt and its relation to their self-destructive behavior. Frequently, dreams provided the first indication of their lingering guilt about combat actions. One veteran who had killed prisoners of war stated that everyone had done it and that he was not troubled by his behavior. However, he dreamed repetitively of being killed in the same way he had killed the prisoners. Another veteran, who had passively witnessed a rape and murder for which he felt no conscious guilt, dreamed recurrently that he was carrying the body of a dead girl and was unable to find a place to bury her.

The need for punishment based on combat guilt or survivor guilt was not the only motivation for suicide. For some veterans, the sense of having been transformed by combat experiences into a "murderer," in danger of again losing control of feelings of aggression and rage, was a significant motivating factor.

Our analysis established both anxiety and depression as significantly related to postcombat suicide attempts. The logistic regression analysis, however, did not confirm that anxiety is a significant predictor of suicidal behavior among veterans with PTSD and suggested that depression plays a role which is clearly secondary to that of guilt about combat actions. It is worth noting that we did not have a single case in which a veteran who experienced anxiety, depression, or both but did not show combat-related guilt had made a suicide attempt.

Many psychiatric disorders—such as depression, alcoholism, schizophrenia, and, most recently, panic disorder—have been shown to be associated with an increased risk for suicide and/or attempted suicide (32–35). In the past two decades, research interest has increasingly focused on understanding why some patients in high-risk diagnostic categories are suicidal while most are not. Intense affective states, such as hopelessness in depression, grief related to loss in alcoholism, or fear of disintegration in schizophrenia, have been found to be significant in making this distinction (17, 36, 37). In the case of veterans with PTSD, our findings indicate that intense combat-related guilt is the most significant explanatory factor.

All the veterans we studied had had considerable combat experience in Vietnam, and all were diagnosed as having PTSD approximately 15 years later. Since almost 20% of our veterans with PTSD had made suicide attempts and another 15% showed sustained preoccupation with suicide (and neither group had a precombat history of suicidal preoccupation or behavior), PTSD emerges as a psychiatric disorder with considerable risk for suicide, at least among this group. The overwhelming presence of guilt related to combat among the veterans who were suicidal points to the need for clinical attention to such guilt in both the evaluation and the treatment of veterans with PTSD.

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# Posttraumatic Stress Disorder After a School Shooting: Effects of Symptom Threshold Selection and Diagnosis by *DSM-III*, *DSM-III-R*, or Proposed *DSM-IV*

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*Objective: The purpose of the study was to investigate the effect of symptom threshold and criteria set selections on the diagnosis of posttraumatic stress disorder (PTSD) in adults and children exposed to a man-made disaster and determine how well* DSM-III *and its successors agree. Method: Data gathered in the course of a voluntary clinical screening for PTSD in 66 adults and 64 children 6 to 14 months after exposure to a school shooting were analyzed according to* DSM-III, DSM-III-R, *and proposed* DSM-IV *criteria for PTSD diagnosis and cluster endorsement using liberal (occurring at least a little of the time), moderate (occurring at least some of the time), and conservative (occurring at least much or most of the time) symptom thresholds. Results: Within* DSM-III, DSM-III-R, *and proposed* DSM-IV, *selection of liberal, moderate, and conservative symptom thresholds had robust effects on rates of diagnoses; liberal thresholds allowed the greatest frequencies of diagnosis. Compared with* DSM-III *and proposed* DSM-IV, DSM-III-R *generally diagnosed the fewest cases. Agreements between* DSM-III-R *and proposed* DSM-IV *were good, while agreements between* DSM-III *and its successors varied for children and adults. Conclusions: Diagnostic rates and agreements were complexly influenced by interactions among thresholds and revisions in symptom clusters. The present study suggests that attempts to refine PTSD classification consider specification of symptom threshold intensity and supports the view that modification of criteria sets be undertaken with caution.*

(Am J Psychiatry 1991; 148:592–597)

The complex relationship between extreme life events and the enduring psychological changes that they induce has been recognized for adults and children since the early days of modern psychiatry (1, 2). Yet, until the publication of *DSM-III*, diagnostic schema had not reflected this association. *DSM-III* newly specified posttraumatic stress disorder (PTSD) as a syndrome with unique constellations of symptoms and a course characterized by biphasic clusters of reexperiencing and avoidant symptoms and a variety of miscellaneous symptoms, including arousal.

Soon after the publication of *DSM-III*, *DSM-III-R*, its revised form currently in use, expanded the definition of the concept of stressor and altered and rearranged symptoms in all clusters. Major modifications expanded the ranges of items in the reexperiencing and avoidance clusters, required an increase in the number of avoidant symptoms from one to three, revised the miscellaneous criteria to reflect a more unitary dimension of arousal (3), and included items to represent PTSD in children (4, 5). Alterations contemplated by the *DSM-IV* Committee on Posttraumatic Stress Disorder would reduce the number of symptoms required in the avoidant cluster from three to two and move physiological reactivity from the arousal to the reexperiencing cluster (R.J. McNally, personal communication, May 10, 1990).

Revising diagnostic criteria, unless justified by solid empirical evidence or good agreement between criteria sets, could frustrate researchers and clinicians by shifting operational definitions and making studies and pa-

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tients difficult to compare (6, 7). To our knowledge, there has been no report of how revisions affect the frequency of the PTSD diagnosis or how well *DSM-III* and its successors agree.

In addition, categorical schema, such as *DSM-III-R*, oblige diagnosticians to set an arbitrary point, or threshold, when counting as present or absent a symptom that may in reality exist along a continuum of intensity. It has been noted for other disorders that significant differences in diagnosis and frequency can result from differences in where on this continuum such thresholds are set (6, 8, 9). To our knowledge, there has been no report of the effect of symptom threshold selection on rates of the diagnosis of PTSD.

In this paper, we study the influences of selection of criteria set and symptom threshold on frequencies of the diagnosis of PTSD in the aftermath of a man-made disaster.

## THE INCIDENT

As part of a daylong, area-wide terror spree, a woman with a psychiatric history, known locally as a baby sitter, entered a closely knit elementary school attended by 310 children in an upper-middle-class suburb. In a boys' washroom she wounded one young child and threatened two others with one of several handguns. In a second-grade classroom she killed one child and wounded five others while classmates watched. Students and teachers in adjacent classrooms heard the shots, and many saw wounded children. The woman then left the school grounds, but because her whereabouts were unknown, the police kept the children in the school, under their desks and separated from their parents, for up to 3 hours. Teachers maintained calm and attended to the bloody wounded until emergency help came. Siblings in other area schools were also kept indoors. Fear was generally sustained throughout the day until information of the woman's suicide at a nearby home was made known (10).

From the first hours through days and weeks after the shooting, mental health professionals provided a variety of mental health services to school officials, teachers, parents, and children. Children had repeated occasions in their classrooms to abreact their fear and anxiety and reappraise the event. In addition, many sought a variety of treatments privately or through community agencies.

## METHOD

Because of the potentially large size of the cohort relative to available resources and limited access to the victims, we designed a screening for PTSD, in collaboration with school officials, directed toward identifying symptomatic individuals. This activity was divided into phases of community negotiations and project design, data collection, clinical data analysis, clinical feedback, and data research analysis. Although our basic aim and permission to work in the community were based on a clinical screening, we felt that systematic methodology might enhance the quality of the intervention. We therefore designed as much such rigor into the project as possible. An attempt was made to select diagnostic instruments that had been published or were already used by investigators. Consent was obtained from subjects to use only pooled data for research purposes. Thus, as we responded clinically, we also accumulated a database of preevent, event, and postevent measures (E.D. Schwarz, unpublished data, 1989).

A total of 141 adults and children were screened, all of whom had been exposed in varying degrees to the shooting and had received varying amounts and types of mental health services. Data from 11 adults were incomplete, leaving a study group of 66 adults and 64 children. Forty-two percent (N=10) of the children in the classroom, 13% (N=9) of those in the same wing, 41% (N=32) of those in the rest of the school, and 11% (N=13) of those off school grounds or on a field trip participated, for a mean of 21% of the total school population. Fifty percent (N=32) of the children in the study group were girls, and the mean age of the children was 8.6 years (range=5–14). At the time of the shooting 80% (N=51) had been in the school or on the grounds (16% [N=10] in the classroom, 14% [N=9] in the wing, and 50% [N=32] elsewhere on the grounds), and 20% (N=13) had been out of the area. Eighty-six percent (N=57) of the adults were women, and the mean age of the adults was 38 years (range=25–66). At the time of the shooting 20% (N=13) had been in the school or on the grounds, 50% (N=33) within a mile, and 30% (N=20) out of the area.

Adults within a mile of the shooting rushed to the scene as the news spread. Many knew the victims or their families, and a few knew the perpetrator or her family. Although some participants in the child and adult study groups were family members (e.g., siblings, spouses), they were included as independent subjects to provide a sufficiently large group for statistical analysis in this study. Later studies will examine the groupings separately.

One subgroup of 24 adults, representing about 70% of the people in the building at the time, changed their location within the building and grounds during the ordeal. The subgroup consisted of teachers and other school personnel who volunteered for a clinical screening 6 to 8 months after the shooting. The remaining 42 adults were parents who enrolled their children in the clinical screening. Children and their parents were screened 8 to 14 months after the event. All participants reported symptom onset soon after the shooting, well within the 6 months required to exclude *DSM-III* and *DSM-III-R* diagnoses of delayed PTSD, and they reported symptom duration for 6 months or more, which met *DSM-III* criteria for chronic PTSD.

The Reaction Index, a 20-item, *DSM-III*-based inventory of PTSD symptoms (11), was selected for the

**TABLE 1. Frequency of PTSD Diagnosis and Symptom Clusters in Witnesses to a School Shooting, According to Different Diagnostic Criteria and Symptom Thresholds**

| | *DSM-III* | | | | | | *DSM-III-R* | | | | | | Proposed *DSM-IV* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Liberal | | Moderate | | Conservative | | Liberal | | Moderate | | Conservative | | Liberal | | Moderate | | Conservative | |
| Group and PTSD Variable | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| Adults (N=66) | | | | | | | | | | | | | | | | | | |
| Diagnosis | 34 | 52 | 11 | 16 | 3 | 4 | 26 | 39 | 12 | 19 | 2 | 3 | 36 | 54 | 16 | 24 | 4 | 6 |
| Cluster | | | | | | | | | | | | | | | | | | |
| Reexperience | 64 | 97 | 51 | 77 | 34 | 52 | 64 | 97 | 53 | 81 | 37 | 56 | 64 | 97 | 54 | 82 | 38 | 58 |
| Avoidance | 37 | 56 | 17 | 26 | 11 | 16 | 33 | 50 | 13 | 20 | 5 | 7 | 43 | 65 | 21 | 32 | 11 | 16 |
| Arousal | 63 | 96 | 40 | 61 | 24 | 36 | 52 | 80 | 30 | 46 | 11 | 16 | 46 | 70 | 27 | 41 | 7 | 11 |
| Children (N=64) | | | | | | | | | | | | | | | | | | |
| Diagnosis | 58 | 91 | 39 | 61 | 10 | 16 | 32 | 50 | 17 | 27 | 5 | 8 | 41 | 64 | 26 | 41 | 6 | 9 |
| Cluster | | | | | | | | | | | | | | | | | | |
| Reexperience | 63 | 98 | 57 | 89 | 33 | 52 | 63 | 98 | 59 | 92 | 35 | 55 | 63 | 98 | 58 | 90 | 35 | 55 |
| Avoidance | 64 | 100 | 58 | 91 | 19 | 30 | 35 | 55 | 19 | 30 | 5 | 8 | 50 | 78 | 37 | 58 | 12 | 19 |
| Arousal | 58 | 91 | 43 | 67 | 16 | 25 | 49 | 77 | 35 | 55 | 12 | 19 | 49 | 77 | 34 | 53 | 11 | 17 |

screenings. This instrument had been used with adults (12) and children (13–15) and validated for both groups. Correlations of 0.90 and above have been reported between the Reaction Index and clinically confirmed PTSD (11). The original investigators provided us with a current version and scoring (R.S. Pynoos and K. Nader, personal communication, July 28, 1988). A children's version, reworded for this particular study by one of the original investigators (K. Nader, personal communication, Dec. 12, 1988), was administered as part of the structured clinical interview conducted by school psychologists and social workers, who rehearsed with videotapes to ensure uniformity. All of the adults completed a self-report version of the instrument (available on request from the authors). Adding the scores of individual items in the Reaction Index yields a continuous *DSM-III*-based index, interpreted as an estimate of the severity of PTSD; the estimate ranges from absent or doubtful (0–11) to mild (12–24), moderate (25–39), and severe (40 and above).

Although we used the index to determine severity in the clinical screenings, we wanted to examine the diagnostic process by using the more universally available *DSM-III* and its successors and determine their sensitivities and the agreement among them. For these separate analyses, the Reaction Index was treated as a symptom checklist questionnaire, and items required for *DSM-III-R* criteria were added, also allowing interpretation according to proposed *DSM-IV*. When exact correspondences were absent, Reaction Index items were collapsed or expanded to conform with criteria set items. Using computer algorithms, we then grouped symptoms into the reexperiencing, numbing/avoidance, and miscellaneous/arousal clusters according to *DSM-III* and its successors.

In addition, we wanted to examine the effects of varying thresholds for counting symptoms as present or absent. Since participants rated each Reaction Index item as present from "none of the time" to "most of the time" along a 5-point Likert scale, threshold levels could be set for each symptom to yield categorical data. The liberal threshold was set when a symptom was reported to occur at least a little of the time. The moderate threshold was set if a symptom was experienced at least some of the time. The conservative threshold was assigned to symptoms endorsed as occurring much or most of the time. This method allowed diagnoses to be made according to three symptom thresholds in each of the three criteria sets.

## RESULTS

### *Threshold and Criteria Set Effects*

*Threshold effects.* Table 1 shows how percentages of patients diagnosed and clusters endorsed dramatically dropped as symptom thresholds were set more conservatively for all criteria sets.

*Criteria set effects. DSM-III-R* was generally the strictest, yielding the fewest diagnoses, except for adults at moderate symptom thresholds, where *DSM-III* was the strictest (table 1). *DSM-III* yielded the highest rates of diagnosis for children, and proposed *DSM-IV* yielded the highest rates for adults.

Reexperiencing cluster endorsements were most frequent and increased between *DSM-III* and its successors. Compared to *DSM-III*, lower rates of endorsement in *DSM-III-R* of avoidance and arousal clusters were associated with lower frequencies of PTSD diagnosis. Compared to adults, children's endorsements of *DSM-III* avoidance clusters were significantly greater at liberal ($\chi^2=36.78$, df=1, $p<0.005$) and moderate ($\chi^2=52.69$, df=1, $p<0.005$) thresholds, leading to significantly more frequent diagnoses of PTSD at liberal ($\chi^2=23.33$, df=1, $p<0.005$) and moderate ($\chi^2=22.93$, df=1, $p<0.005$) thresholds. Compared to *DSM-III-R*, proposed *DSM-IV* had greater frequencies of both avoidance cluster endorsements and diagnoses of PTSD. Moving the physiological reactivity symptom

**TABLE 2. Agreement Among *DSM-III*, *DSM-III-R*, and Proposed *DSM-IV* Criteria for PTSD**[a]

| | Liberal Threshold | | | | Moderate Threshold | | | | Conservative Threshold | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *DSM-III-R* | | Proposed *DSM-IV* | | *DSM-III-R* | | Proposed *DSM-IV* | | *DSM-III-R* | | Proposed *DSM-IV* | |
| Group and Criteria | Agreement | Kappa | Agreement | Kappa | Agreement | Kappa | Agreement | Kappa | Agreement | Kappa | Agreement | Kappa |
| Adults | | | | | | | | | | | | |
| *DSM-III* | Fair | 0.44 | Poor | 0.31 | Good | 0.70 | Fair | 0.49 | Poor | 0.38 | Poor | 0.30 |
| *DSM-III-R* | | | Good | 0.65 | | | Good | 0.69 | | | Excellent | 0.79 |
| Children | | | | | | | | | | | | |
| *DSM-III* | Poor | 0.19 | Poor | 0.31 | Poor | 0.38 | Fair | 0.55 | Good | 0.74 | Good | 0.68 |
| *DSM-III-R* | | | Good | 0.72 | | | Good | 0.69 | | | Excellent | 0.90 |

[a] For poor agreement, kappa=0.00–0.39; fair, kappa=0.40–0.59; good, kappa=0.60–0.74; and excellent, kappa=0.75–1.00 (16, 17).

from the arousal cluster in *DSM-III-R* to the reexperiencing cluster in proposed *DSM-IV* decreased endorsements of arousal clusters but had only small net effects on reexperiencing clusters and overall rates of diagnosis.

### *Agreements Among Criteria Sets*

Table 2 shows kappa coefficients that represent indices of agreement for PTSD diagnosis corrected for chance correspondences (16) and interpreted according to the criteria of Cicchetti and Sparrow (17); the kappa coefficients were calculated pairwise among *DSM-III* and its successors at the three symptom threshold levels. Diagnostic agreements between *DSM-III-R* and proposed *DSM-IV* were good to excellent for adults and children. At the moderate thresholds, for example, only 9% of adults (N=2) and 19% of children (N=8) diagnosed by proposed *DSM-IV* were excluded by *DSM-III-R*, while 7% of *DSM-III-R* diagnosed adults (N=1) were excluded by proposed *DSM-IV*.

By contrast, agreements between *DSM-III* and both of its successors varied according to threshold levels and between adults and children. At conservative thresholds, agreement was good for children but poor for adults. For example, two of the three adults diagnosed by *DSM-III* were excluded by *DSM-III-R* and proposed *DSM-IV*, while one of three diagnosed by *DSM-III-R* and two of three by proposed *DSM-IV* were excluded by *DSM-III*.

At liberal and moderate thresholds, however, agreements between *DSM-III* and *DSM-III-R* were poor for children but fair to good for adults. For example, at moderate thresholds, 18% of adults (N=3) and 56% of children (N=34) diagnosed by *DSM-III* were excluded by *DSM-III-R*, while 7% of adults (N=1) diagnosed by *DSM-III-R* were excluded by *DSM-III*. Agreements between *DSM-III* and proposed *DSM-IV* were not good. For example, at moderate thresholds 27% of adults (N=4) and 36% of children (N=22) diagnosed by *DSM-III* were excluded by proposed *DSM-IV*, while 14% of adults (N=3) and 4% of children (N=2) diagnosed by proposed *DSM-IV* were excluded by *DSM-III*.

## DISCUSSION

This report, derived from data collected in the aftermath of a school shooting, examines the effects of criteria set and symptom threshold selections on the self-reported frequency of PTSD in cohorts of 64 children and 66 adults.

First, the results demonstrated consistent and robust effects of symptom thresholds on frequencies of diagnosis across all criteria sets and symptom clusters. For example, the number of adults diagnosed by *DSM-III-R* at liberal thresholds (experiencing symptoms at least a little of the time) was 13-fold greater than that by conservative thresholds (experiencing symptoms much or most of the time).

Second, the data indicated that diagnostic criteria set selection influenced rates of diagnosis. As with autism (18), bulimia (19), and schizophrenia (20), *DSM-III-R* was the most restrictive, with one exception. Generally, *DSM-III-R* was the most restrictive because stricter criteria in the avoidance and arousal clusters outweighed easier criteria (because of an expanded range of symptoms) in the reexperiencing cluster. But for adults at moderate thresholds the balance went the other way, and *DSM-III* was most restrictive.

*DSM-III* was least restrictive for children because they endorsed at least one of the three items in its avoidance cluster more abundantly than did adults. Proposed *DSM-IV* was the least restrictive for adults. Paradoxically, adults met proposed *DSM-IV* avoidance cluster criteria (requiring two symptoms) at slightly higher rates than they did *DSM-III* criteria (requiring only one symptom). This may derive from the observation that *DSM-III* included only three items in its avoidance cluster, while its successors expanded the range of items to seven. Compared to *DSM-III*, while the more stringent requirement of *DSM-III-R* for endorsements of three items reduced the number of adults who met the avoidance cluster criteria, the stipulation of proposed *DSM-IV* of only two avoidance symptoms from the expanded item range increased their number. The net effect of expanding the range of items and requiring only two in the avoidance cluster was greater for adults than for children.

Third, diagnostic agreements between *DSM-III-R* and proposed *DSM-IV* were good to excellent for adults and children at all thresholds, with proposed *DSM-IV* essentially functioning as a liberalization of *DSM-III-R*. However, patterns of agreement between *DSM-III* and its successors were poorer and less intelligible. The poor agreement between *DSM-III* and its successors for the few most severely affected adults detected by conservative thresholds is reason for serious concern and bears examination with larger cohorts. In addition, at moderate thresholds, over half of the children diagnosed by *DSM-III* were excluded by *DSM-III-R* and over a third by proposed *DSM-IV*. One explanation is that children's greater rates of endorsement of avoidance symptoms at liberal and moderate thresholds were apparently sufficient to meet the less stringent avoidance criteria of *DSM-III*, leading to greater rates of diagnosis and poorer agreements with its successors.

In sum, the results showed that sometimes troublesome and confusing diagnostic incongruities among criteria sets that differed for adults and children resulted from complex interactions among thresholds and revisions of items within clusters.

Fourth, the data invited more detailed comparisons of adults with children. Children's significantly greater rates of the PTSD diagnosis at *DSM-III* liberal and moderate symptom thresholds were associated with higher rates of endorsement of avoidance clusters by children. Additional analyses reported elsewhere (21) revealed differences between children and adults in frequencies and patterns of endorsement of individual symptoms. For both groups diagnoses were associated with recalled intensity of emotional states experienced the day of the shooting; there were no associations between diagnosis and proximity to the shooting, acquaintance with the victims or the perpetrator, age, or sex.

Fifth, this paper illustrates that despite the unpredictable nature of a disaster, data can be systematically collected while clinical services are provided.

However, the current study must be regarded as an attempt to systematize observations made in a unique natural setting rather than a well-controlled, preplanned investigation, and limitations to its generalizability must be discussed fully. The study group in this report did not represent a random sample. Twenty-one percent of the available children, at least one of their parents, and most of the school personnel in the building that day did participate; and the study group represented all categories of exposure, albeit not uniformly. However, school personnel and parents volunteered themselves and the children, while children may have exercised little choice. Adults with high avoidance may have abstained from participating altogether, lowering endorsement of avoidance symptoms and frequency or severity of PTSD seen in adults or possibly their children. On the other hand, if volunteering selected a healthier group of adults, their children may have represented a more general, less selected, population. Therefore, children may have suffered other disorders not reported here more than adults did. Furthermore, more children with existing problems may have been enrolled in the screening because of parental concerns. Even when large numbers of people are affected, attempts at systematic research have often been compromised by small, self-selected, and nonrepresentative groups because many victims are often reluctant to participate (22, 23). Unfortunately, no screening or data collection of any kind would have been possible in this community had it been primarily for the purpose of research or had attempts been made to select a random, more uniform sample.

The use of a self-report measure for adults and a structured clinical interview for children may not yield comparable types of data. Children and adults may differ in their ability to report general or specific types of symptoms. For example, children may have revealed avoidance symptoms more easily. Because they were members of a traumatized community, the interviewers of the children may themselves have suffered PTSD symptoms, if not by exposure, then perhaps by contagion. Whether this would have resulted in underreporting of different symptoms, overreporting, or both is unclear. The use of indigenous interviewers, however, was part of a collaborative effort with school officials and contributed to the restoration of communal sense of control, order, and competence. Not only did their use allow more efficient deployment of limited resources, but we believe that without this arrangement a "trauma membrane" (23, 24) would have obstructed the screenings altogether.

For both groups, while avoidance symptoms could preclude self-reporting in a one-time screening, yielding lower frequencies of PTSD, these symptoms may become more apparent over several visits to a clinician, increasing the likelihood of diagnosis in an actual clinical situation and yielding more diagnoses. Therefore, the decreases in diagnoses based on increasing the number of avoidance symptoms required by *DSM-III-R* might not be as dramatic in the clinical situation.

In addition, Horowitz (25) suggested that stress-related avoidance and intrusive symptoms may not coexist, as suggested by present criteria, but alternate over time. The disorder may remain latent until activated by internal or external cues, and studies that are not longitudinal may elicit clinical pictures reflecting different phases of the natural history of PTSD.

In conclusion, the classification of a disorder ultimately derives from replicable identifications of clinical subgroups having relatively homogeneous presentations, courses, treatment responses, and outcomes (26), as well as clarification of its biopsychosocial pathogenesis and boundaries with normality. Because opportunities to study reactions to disasters may be relatively rare, having a reliable classification readily accessible would increase chances for such studies. Without a uniform standard of measure, variability in diagnoses can be due to variance in criteria threshold, as well as to differences in the criteria themselves. Until we can better define PTSD in terms of external criteria to elaborate further the significance of our measures (27), it would seem reasonable to use stable criteria sets and specify symptom thresholds.

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# The Assessment and Treatment of Performance Anxiety in Musicians

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*Objective: Performance anxiety in musicians may be severe enough to require intervention but has been the subject of relatively little clinical research. The authors' objectives were to describe the results of a comprehensive clinical and laboratory assessment and to perform a double-blind, placebo-controlled study comparing buspirone, cognitive-behavior therapy, and the combination of these treatments for performance anxiety. Method: Ninety-four subjects were recruited by mass media announcements and were seen in a university-based outpatient psychiatric clinic. Assessments were 1) questionnaires for all 94 subjects, 2) diagnostic interview of 50 subjects, and 3) laboratory performance of 34 subjects. Treatment conditions were 1) 6 weeks of buspirone, 2) 6 weeks of placebo, 3) a five-session, group cognitive-behavior therapy program with buspirone, or 4) the cognitive-behavior therapy program with placebo. Treatment outcome measures included subjective anxiety ratings and heart rate measures during a laboratory performance, a questionnaire measure of performance confidence, and a blind rating of musical performance quality. Results: All subjects fulfilled criteria for* DSM-III-R *social phobia. Of the 15 full-time professional musicians, ten had tried propranolol and three had stopped performing. Most of the subjects had substantial anxiety and heart rate increases during laboratory speech and musical performances. Cognitive-behavior therapy resulted in statistically significant reductions in subjective anxiety, improved quality of musical performance, and improved performance confidence. Buspirone was not an effective treatment. Conclusions: Cognitive-behavior therapy is a viable treatment approach for performance anxiety in musicians.*

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The medical and psychological problems of musicians have been the subject of increasing interest and systematic investigation (1–3). Of 2,212 professional classical musicians surveyed by the International Conference of Symphony and Opera Musicians (4, 5), 24% reported a problem with performance anxiety (stage fright) and 16% described the problem as severe. Smaller studies have also found performance anxiety to be common in musicians (6, 7) and that amateur musicians and students had relatively more performance anxiety than professionals (8). Performance anxiety in musicians may be conceptualized as a form of social phobia, and low but statistically significant correlations have been reported between anxiety during musical performances and in other social situations (8).

The International Conference of Symphony and Opera Musicians survey (4, 5) indicated that β blockers were by far the most common form of treatment used by professional musicians: 27% reported daily or occasional use. Of these, 19% used β blockers daily, as prescribed, presumably for hypertension, and 11% used them occasionally, as prescribed. The remaining 70% were occasional users who took β blockers without prescription. This indicates that a substantial proportion of professional musicians are illicitly using β blockers without medical supervision. Other treatments had been tried much less frequently. Of the musicians who reported severe performance anxiety, only 25% had tried what the survey termed "psychological

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counseling," and the reported success rate was 60%. A small proportion, 11%, reported that they had visited a general practitioner for assistance, and only 27% said they found the visit useful.

Despite the popularity of β blockers, reviews of controlled research have concluded that these drugs have an equivocal impact on performance anxiety (1, 9). Controlled trials have demonstrated that β blockers resulted in a significantly greater lowering of heart rate and tremor than placebo (10–13). The effect of β blockers on subjective anxiety is less impressive: some studies found a modest effect (11), but others found no difference from the effects of placebo (10, 12, 13). Benzodiazepines are effective for subjective anxiety but have an adverse effect on the quality of musical performance because they impair psychomotor functioning (12).

Buspirone has a number of potential advantages as a treatment for performance anxiety. It has been demonstrated to reduce anxiety (14), although its peak effect occurs after about 3 weeks of continuous administration (15). Unlike benzodiazepines, buspirone does not impair psychomotor performance (16) or memory (17); few other limiting side effects have been reported (18).

Behavior therapists have emphasized the importance of systematic exposure to feared stimuli in the treatment of phobias. Such exposure is conceptualized as leading to extinction of the conditioned fear (19). Indirectly supporting this idea is the finding of a negative correlation between performance anxiety and years of playing in public among professional musicians (8). An alternative explanation for this relationship, however, is that musicians who experience more anxiety on performing give up the occupation, leaving a preponderance of older musicians who experience less anxiety (8). The notion that exposure always leads to extinction of fear is contradicted by the fact that many musicians continue to suffer from performance anxiety despite years of experience and recent findings of a lack of relationship between performance anxiety and age (7). Furthermore, problems in the clinical application of exposure therapy to social phobia, such as difficulties specifying graduated tasks and prolonging exposure, have been noted (20).

In a study of cognitive aspects of musical performance anxiety (8), negative cognitions were shown to have a positive correlation and positive cognitions were found to have a negative correlation with performance anxiety. This association between performance anxiety and cognitive style suggests that negative cognitions may perpetuate anxiety that would otherwise be extinguished with exposure and that a treatment approach for musical performance anxiety based on a strategy of restructuring cognitions may be effective.

A cognitive-behavior therapy program combining exposure and cognitive therapy for pianists has been developed and tested. Comparing three weekly sessions of exposure therapy alone with combined cognitive and exposure therapy with 53 pianists, Kendrick et al. (21) found no statistically significant differences after treatment, but both types of therapy were more effective than a control condition in reducing anxiety measured 5 weeks after termination of treatment. The addition of cognitive therapy proved to be superior to exposure therapy alone in both a subjective measure of performance anxiety and a measure of signs of anxiety during performance. This suggests that cognitive therapy is a useful adjunct to exposure therapy but that 3 weeks may be insufficient for subjects to learn to use the approach.

The purposes of this study were 1) to study the psychological characteristics and previous treatment of musicians with performance anxiety, 2) to complete a laboratory assessment of subjective and physiological responses to a speech and a musical performance, and 3) to perform a double-blind, placebo-controlled trial of buspirone with and without cognitive-behavior therapy for performance anxiety in musicians.

## METHOD

### *Subjects*

Subjects recruited through the mass media were briefly interviewed by telephone. Those reporting a problem with performance anxiety were sent a set of questionnaires. To be included, the respondent had to report that performance anxiety impaired his or her performance or that performance anxiety resulted in some avoidance of performance situations. In addition, respondents were required to score 8 or more on the Personal Report of Confidence as a Performer (22). Of the 99 subjects who returned questionnaires, 40 men and 54 women met these criteria. Their mean age was 37.5±11.6 years, and their age at onset of performance anxiety was 16.0±8.7.

After returning the Personal Report of Confidence as a Performer, those subjects 18–60 years old who were interested in participating in treatment and indicated that they had no serious medical disorders were invited to undergo further assessment. Subjects considered for inclusion in the laboratory assessment and treatment study were interviewed by using the Structured Clinical Interview for DSM-III-R (SCID) (23). To be eligible for participation, subjects had to meet *DSM-III-R* criteria for social phobia with regard to at least a definable subset of performance situations, such as solo performing. Two subjects also met criteria for the generalized subtype of social phobia.

Of the 94 subjects who met severity criteria for performance anxiety, 14 were not eligible for the treatment study as a result of medical problems (seven subjects), psychiatric disorders (one had current anorexia nervosa and one had current methadone maintenance), or age (three were older than 65 years and two were younger than 18). Of the 80 remaining subjects who were invited for a diagnostic interview, 30 declined, did not respond to further inquiries, or did not attend scheduled appointments. Of the 50 subjects interviewed, one was ineligible as a result of current alcohol dependence and one was ineligible as a result of marijuana dependence and agoraphobia. Fourteen eligible subjects declined further participation. Of those who stated a specific reason for declining participation other than travel distance, seven did not want to take medication, two did not want to discontinue propranolol, and one did not want cognitive-behavior therapy. Therefore, 34 subjects were eligible for and elected to participate in the laboratory assessment and treatment program. These 34 subjects were not significantly different from the larger group of 94 subjects on any variable. Written informed consent was obtained from all participating subjects.

### *Assessment*

The questionnaire assessment included demographic information, professional status, consequences of performance anxiety, and attempted treatments. Standardized measures included the Personal Report of Confidence as a Performer (22), the trait subscale of the State-Trait Anxiety Inventory (24), the Self-Statement Questionnaire (8), and the Fear Survey Schedule (25). The Social Avoidance and Distress Scale and the Fear of Negative Evaluation Scale (26) were also administered.

The Personal Report of Confidence as a Performer (22) is a questionnaire with 30 true-false items concerning confidence and anxiety regarding musical performance developed from the Personal Report of Confidence as a Speaker (27). The questions survey cognitive, behavioral, and somatic aspects of performance anxiety. Questions include, "My thoughts become jumbled and confused when I perform before an audience," "I always avoid playing solos in public if possible," and "My hands or legs tremble when I play." A higher score indicates more anxiety and less confidence.

The Self-Statement Questionnaire (8) subscales concerning negative cognitions (six items) and positive cognitions (three items) were used to construct a weighted composite score to assess the effect of treatment. Questions include, "I'm almost sure to make a dreadful mistake, and that will ruin everything," and "I'll just concentrate on staying relaxed." A higher score indicates more negative and less positive cognitions.

The Fear Survey Schedule (25), including 63 common phobias, was subdivided into five subscales: 1) fear of negative evaluation, 2) social anxiety, 3) fear of bodily harm, 4) agoraphobia, and 5) fear of animals and insects. Each item had one of four responses (no fear=0, extreme fear and avoidance=3), and a mean score was used for each subscale.

Laboratory assessments were made before and after treatment. Each subject selected and performed a piece of music 4–6 minutes long in front of an audience of three to ten members. Each subject also gave a speech. The speech was also 4–6 minutes long and could be on any topic. The order of the musical performance and speech was randomized for each subject before treatment, and the same order was used after treatment. The musical performance and the speech were separated by approximately 15 minutes. With the exception of one of us (D.B.C.), the audience members were not known to the subjects, and subjects did not participate as audience members. Immediately after the performance and the speech, each subject was asked to rate his or her anxiety on a 10-point scale (1=no anxiety, 10=extreme anxiety). Each subject's heart rate was monitored continuously throughout the performance and speech by using an ambulatory monitor (Vitalog Corporation, Mountain View, Calif.) (28). Starting 5 minutes after the final performance, we obtained a 15-minute resting heart rate. All performances were audiotaped, and any information that might allow raters to guess the time of the performance or experimental condition of the subject were erased. Performances before and after treatment were presented in random order and compared by raters who were blind to order and the subject's experimental condition. They used a scale on which −2=much worse than the comparison performance and 2=much better than the comparison performance. These raters did not participate in any other aspect of data collection or analysis.

The Social Avoidance and Distress Scale, the Fear of Negative Evaluation Scale (28), the Personal Report of Confidence as a Performer, and the Self-Statement Questionnaire were administered before and after treatment. One month after the termination of treatment, subjects again completed the Personal Report of Confidence as a Performer.

Indexes of improvement and endpoint functioning were constructed by using scores on the Personal Report of Confidence as a Performer. Subjects were classified as improved if they had a reduction of 5 or more points from baseline to follow-up. Subjects were classified as having good endpoint functioning if they had a score of 7 or lower at follow-up. A score of 7 was selected as the criterion for good endpoint functioning because a score of 8 or higher was required for entry into the study. Therefore, subjects achieving a score of 7 or lower would no longer be considered to have performance anxiety of sufficient severity to warrant treatment.

### *Treatment*

Subjects were randomly assigned to one of four treatment conditions: 1) cognitive-behavior therapy with placebo (nine subjects), 2) cognitive-behavior therapy with buspirone (eight subjects), 3) buspirone alone (nine subjects), and 4) placebo alone (eight subjects).

Cognitive-behavior therapy was given to three groups of five or six subjects each. The program was administered in five weekly meetings. Appendix 1 describes the program. Treatment was based, in part, on the model developed by Kendrick et al. (21) but was substantially expanded. The program identified cognitive distortions, provided coping models, and encouraged exposure to feared performance situations. All groups were conducted by one of us (D.B.C.).

Buspirone in 5-mg tablets or placebo was initially prescribed three times/day; the dose was increased as tolerated to a maximum total dose of 12 tablets/day. The therapeutic effects were assessed after 6 weeks of continuous use. Side effects were monitored throughout treatment and systematically assessed after treatment. The subject and the prescribing physician were blind to the drug condition until the experiment was completed. After 6 weeks of buspirone or placebo, medication was discontinued and the subject was monitored for a 1-month follow-up period.

### *Statistical Methods*

For most outcome analyses, repeated measures analysis of variance was used. Three analyses were completed for each variable: 1) cognitive-behavior therapy groups (i.e., those given cognitive-behavior therapy with buspirone and those given cognitive-behavior therapy with placebo) were compared with medication groups (i.e., those given buspirone alone and those given placebo alone), 2) buspirone groups (i.e., those given cognitive-behavior therapy with buspirone and those given buspirone alone) were compared with placebo groups (i.e., those given cognitive-behavior therapy with placebo and those given placebo alone), and 3) interaction analyses were conducted for the four conditions. Separate analyses were carried out comparing the subjects before and after treatment and, where applicable, comparing the subjects after treatment and at 1-month follow-up.

Subjective anxiety for the musical performance in the laboratory was correlated with audience size ($r=0.52$, $df=32$, $p<0.01$) and the subject's professional status ($r_s=0.45$, $df=32$, $p<0.01$). Subjective anxiety for the speech was also correlated with audience size ($r=0.47$, $df=32$, $p<0.01$). Therefore, a multivariate repeated measures analysis of covariance was used for the outcome analyses in these cases to control for the relevant correlated variables.

## RESULTS

### *Questionnaire Assessment*

Table 1 lists the characteristics of the 94 subjects as reported on the questionnaire. Of the 15 full-time professional musicians, three had stopped performing as a result of performance anxiety.

The mean±SD score of the 94 subjects on the Personal Report of Confidence as a Performer was 17.6±5.0. Their mean score on the negative thinking subscale of the Self-Statement Questionnaire was significantly positively correlated ($r=0.52$, $df=89$, $p<0.001$) and their mean score on the positive thinking subscale of this measure was significantly negatively correlated ($r=-0.45$, $df=89$, $p<0.001$) with their mean score on the Personal Report of Confidence as a Performer. The subjects' mean score on the trait subscale of the State-Trait Anxiety Inventory was 46.7±11.1; this was positively correlated with their mean Personal Report of Confidence as a Performer score ($r=0.34$, $df=91$, $p<0.001$). The mean score (1.8±0.8) on the fear of negative evaluation subscale of the Fear Survey Schedule was significantly higher than that on any other subscale, including social anxiety (0.7±0.4) ($t=15.9$, $df=93$, $p<0.0001$), fear of bodily harm (0.9±0.5) ($t=11.6$, $df=93$, $p<0.0001$), agoraphobia (0.4±0.3) ($t=18.5$, $df=93$, $p<0.0001$), and fear of animals and insects (0.6±0.4) ($t=16.6$, $df=93$, $p<0.0001$).

As can be seen in table 1, more musicians had tried drinking alcohol as a method of reducing performance anxiety than had tried prescribed medications or psychotherapy. The musicians with different levels of professional status had tried similar treatments, except for β blockers: a significantly larger percentage of full-time professional musicians (67%, N=10) than part-time professionals (37%, N=10), students (13%, N=1), serious amateurs (13%, N=4), or casual amateurs (none) had tried β blockers ($\chi^2=21.9$, $df=4$, $p<0.001$). Other subjects reported the use of phenobarbital (N=1), marijuana (N=2), or cocaine (N=1) for performance anxiety.

**TABLE 1. Characteristics Reported on Questionnaires by 94 Musicians With Performance Anxiety**

| Characteristic | Number | Percent |
|---|---|---|
| Professional status | | |
| Full-time professional | 15 | 16 |
| Part-time professional | 27 | 29 |
| Full-time music student | 8 | 9 |
| Serious amateur | 31 | 33 |
| Casual amateur | 13 | 14 |
| Instrument | | |
| Voice | 27 | 29 |
| Guitar | 24 | 26 |
| Keyboard | 20 | 21 |
| Strings | 11 | 12 |
| Wind and brass | 6 | 6 |
| Percussion | 2 | 2 |
| Miscellaneous | 4 | 4 |
| Consequences of performance anxiety | | |
| Performance impaired | 91 | 97 |
| Avoided performing | 72 | 77 |
| Stopped performing | 18 | 19 |
| Left profession | 10 | 11 |
| Drank alcohol | 39 | 41 |
| Previous treatments | | |
| β Blockers | 24 | 26 |
| Benzodiazepines | 19 | 20 |
| Psychotherapy | 23 | 24 |

**TABLE 2. Side Effects Reported by Musicians With Performance Anxiety Given Buspirone (N=15) or Placebo (N=14)**

| Side Effect | Number of Subjects With Side Effect | |
|---|---|---|
| | Buspirone | Placebo |
| Dizziness or lightheadedness | 11 | 1 |
| Headaches | 6 | 3 |
| Nervousness | 4 | 2 |
| Drowsiness | 3 | 1 |
| Confusion | 3 | 1 |
| Decreased concentration | 3 | 2 |
| Nausea | 4 | 2 |
| Depression | 2 | 0 |
| Anger or irritability | 2 | 2 |
| Insomnia | 2 | 2 |
| Numbness or weakness | 2 | 0 |
| Blurred vision | 2 | 1 |
| Diarrhea | 2 | 1 |
| Excitement | 2 | 2 |
| Dry mouth | 1 | 1 |
| Muscle aches | 0 | 1 |
| Any side effect | 13 | 8 |

### *Diagnostic and Laboratory Assessments*

Fifty subjects were given the SCID. Thirty-one had current and/or past psychiatric diagnoses other than social phobia; 10 of these subjects met criteria for multiple diagnoses. Of the current diagnoses, the most common was simple phobia (N=8), followed by generalized anxiety disorder (N=5), psychoactive substance use disorders (N=2), and agoraphobia (N=1). Of past diagnoses, the most common was major depression (N=20), followed by psychoactive substance use disorders (N=5), panic disorder (N=3), anorexia nervosa (N=1), and bulimia nervosa (N=1).

In the laboratory, subjects reported a mean subjective anxiety level of 7.1 (range=2–10) during the musical performance and 5.6 (range=1–10) during the speech. Subjective anxiety was significantly higher during the musical performance than during the speech ($t=3.2$, $df=32$, $p<0.01$), although musical performance and speech ratings were significantly correlated ($r=0.34$, $df=32$, $p<0.05$).

The subjects' mean heart rate during the musical performance was 111±22 bpm; during the speech it was 104±21 bpm. Their mean heart rate increased substantially over the resting baseline level during the musical performance (by 31.4±16.2 bpm) and during the speech (by 24.1±16.3 bpm). The change in the subjects' mean heart rate from baseline to during the speech was significantly correlated with their subjective rating of anxiety during the speech ($r=0.33$, $df=30$, $p<0.05$), but the corresponding heart rate and anxiety values were not correlated for the musical performance ($r=-0.05$, $df=30$, n.s.). Similar to their subjective rating of anxiety, the subjects' mean heart rate was significantly higher during the musical performance than during the speech ($t=2.21$, $df=31$, $p<0.05$), and their mean heart rates during the musical performance and during the speech were significantly correlated ($r=0.64$, $df=30$, $p<0.01$). The subjects had mean scores of 19.1±7.4 on the Fear of Negative Evaluation Scale and 8.1±7.2 on the Social Avoidance and Distress Scale.

### *Treatment Outcome*

Of the 34 subjects who completed the laboratory assessment and began treatment, 29 (85%) completed treatment. Two of the nine subjects assigned to cognitive-behavior therapy with placebo, none of the eight subjects assigned to cognitive-behavior therapy with buspirone, two of the nine subjects assigned to buspirone only, and one of the eight subjects assigned to placebo only dropped out of treatment. The four treatment groups did not differ significantly in dropout rates ($\chi^2=2.22$, $df=3$, n.s.).

At the end of treatment, the 15 subjects given buspirone were taking a mean of 6.4±2.2 tablets/day (32±11 mg/day, range=15–50 mg/day). The 14 subjects given placebo were taking a mean of 8.6±2.8 tablets/day (range=3–12 tablets), significantly more tablets than were taken by those given buspirone ($t=2.14$, $df=22$, $p<0.05$). Of reported side effects, dizziness or lightheadedness was reported more frequently by subjects taking buspirone than by those taking placebo ($\chi^2=12.6$, $df=1$, $p<0.001$). The two groups did not differ significantly in the occurrence of other side effects (table 2). On discontinuation of the study, one subject taking buspirone reported a headache that resolved without specific treatment. This subject had a history of similar headaches, and whether there was a causal relationship with the discontinuation of buspirone could not be determined. No other problems with discontinuation of buspirone were noted.

The 15 subjects who completed cognitive-behavior therapy had a greater reduction in subjective anxiety during the musical performance after treatment than did those receiving buspirone only or placebo only (table 3). A similar result was noted for subjective anxiety during the speech (table 3). Subjects given cognitive-behavior therapy also showed greater improvement in the quality of the musical performance after treatment (table 3). Significant changes in heart rate, however, were not noted during the musical performance or the speech after treatment. Differences were not demonstrated on the Self-Statement Questionnaire. The scores on the Personal Report of Confidence as a Performer of the subjects given cognitive-behavior therapy were also not significantly different after treatment than before treatment. However, they were significantly better at follow-up than they were after treatment (table 3).

There were few statistically significant differences between the subjects given buspirone and those given placebo. No statistically significant differences were found for change in subjective anxiety during the musical performance or during the speech. These groups also did not differ on the change in quality of musical performance. The change in heart rate was not signifi-

**TABLE 3. Ratings for 29 Musicians With Performance Anxiety Before and After Treatment With Cognitive-Behavior Therapy With Buspirone or Placebo, Buspirone Alone, or Placebo Alone**

| | Treatment | | | | | | | | Multiple Analysis of Covariance | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cognitive-Behavior Therapy With Placebo (N=7) | | Cognitive-Behavior Therapy With Buspirone (N=8) | | Buspirone Alone (N=7) | | Placebo Alone (N=7) | | Cognitive Therapy (N=15) Versus No Cognitive Therapy (N=14)[a] | | | Placebo (N=14) Versus Buspirone (N=15)[b] | | |
| Outcome Measure | Mean | SD | Mean | SD | Mean | SD | Mean | SD | F | df | p | F | df | p |
| Rating of subjective anxiety during musical performance[c] | | | | | | | | | | | | | | |
| Before treatment | 7.4 | 2.6 | 7.8 | 2.4 | 7.6 | 1.6 | 6.3 | 2.5 | | | | | | |
| After treatment | 5.0 | 1.8 | 5.4 | 0.9 | 6.0 | 2.2 | 5.5 | 1.7 | 5.08 | 1, 23 | <0.05 | 0.83 | 1, 23 | n.s. |
| Rating of subjective anxiety during speech[c] | | | | | | | | | | | | | | |
| Before treatment | 5.3 | 2.6 | 7.0 | 2.6 | 5.4 | 2.4 | 4.6 | 1.0 | | | | | | |
| After treatment | 3.0 | 1.8 | 4.1 | 2.4 | 4.4 | 1.9 | 4.0 | 1.4 | 5.74 | 1, 25 | <0.05 | 0.40 | 1, 25 | n.s. |
| Rating of audiotape of musical performance[d] | 1.6 | 0.5 | 0.6 | 0.7 | 0.6 | 0.8 | 0.3 | 1.0 | | — | | | — | |
| Heart rate during musical performance (bpm) | | | | | | | | | | | | | | |
| Before treatment | 115.4 | 28.4 | 111.0 | 16.4 | 107.8 | 20.7 | 111.8 | 29.5 | | | | | | |
| After treatment | 113.1 | 24.9 | 111.5 | 17.7 | 101.0 | 15.7 | 107.8 | 28.1 | 0.38 | 1, 23 | n.s. | 0.00 | 1, 23 | n.s. |
| Heart rate during speech (bpm) | | | | | | | | | | | | | | |
| Before treatment | 103.0 | 21.7 | 116.0 | 25.8 | 95.8 | 16.3 | 99.2 | 19.9 | | | | | | |
| After treatment | 100.0 | 23.2 | 98.9 | 15.8 | 91.2 | 17.0 | 93.2 | 19.3 | 0.33 | 1, 23 | n.s. | 0.80 | 1, 23 | n.s. |
| Self-Statement Questionnaire rating[c] | | | | | | | | | | | | | | |
| Before teatment | 4.0 | 0.6 | 3.6 | 0.9 | 3.8 | 0.3 | 4.1 | 0.5 | | | | | | |
| After treatment | 3.0 | 0.8 | 3.3 | 0.7 | 3.9 | 0.4 | 3.6 | 0.6 | 2.56 | 1, 27 | n.s. | 6.43 | 1, 27 | <0.05 |
| Personal Report of Confidence as a Performer rating[c] | | | | | | | | | | | | | | |
| Before treatment | 16.3 | 3.4 | 15.6 | 4.7 | 18.1 | 4.1 | 20.3 | 3.8 | | | | | | |
| After treatment | 14.6 | 3.9 | 12.0 | 5.8 | 13.4 | 7.2 | 13.0 | 6.5 | 3.09 | 1, 27 | n.s. | 0.04 | 1, 27 | n.s. |
| 1-month follow-up | 5.8 | 3.7 | 9.7 | 3.0 | 11.9 | 9.3 | 15.4 | 4.4 | 5.75 | 1, 22 | <0.05 | 1.36 | 1, 21 | n.s. |

[a] In all significant comparisons, the groups given cognitive-behavior therapy had better ratings than the groups given no cognitive-behavior therapy.

[b] In the one significant comparison, the groups given placebo had better ratings than the groups given buspirone.

[c] A higher rating indicates more anxiety or more negative cognitions.

[d] A higher rating indicates better quality. Significant difference between cognitive therapy and no cognitive therapy (t=2.08, df=25, p<0.05) but not between placebo and buspirone (t=−0.72, df=25, n.s.).

cantly different for the musical performance or the speech. There was a statistically significant change in Self-Statement Questionnaire ratings that favored placebo (table 3). The buspirone groups did not show significantly more change than the placebo groups on the Personal Report of Confidence as a Performer.

The comparison of buspirone and placebo groups was reanalyzed without the five subjects who were taking three or fewer tablets/day at the end of treatment. None of the results were substantially changed, except that the subjects given placebo had better ratings on the Self-Statement Questionnaire (F=8.5, df=1, 21, p<0.01).

When paired comparisons were performed, all statistically significant comparisons among treatment conditions favored cognitive-behavior therapy with placebo. There was a significant interaction between treatment condition and time on the quality of the musical performance (F=3.72, df=3, 25, p<0.05). Subjects given cognitive-behavior therapy with placebo showed significantly more change than those receiving placebo alone (F=3.27, df=1, 12, p<0.05, Scheffé test). There was a significant interaction between treatment condition and ratings on the Self-Statement Questionnaire (F=3.38, df=1, 27, p<0.05), and the subjects given cognitive-behavior therapy with placebo had significantly better ratings than those given buspirone alone (F=3.26, df=1, 12, p<0.05, Scheffé test). There was also a significant interaction between treatment condition and time on change from after treatment to follow-up on the Personal Report of Confidence as a Performer ($F=6.64$, $df=3, 20$, $p<0.01$). Subjects given cognitive-behavior therapy with placebo had significantly better ratings than those given cognitive-behavior therapy with buspirone ($F=3.28$, $df=1, 10$, $p<0.05$, Scheffé test), buspirone alone ($F=3.31$, $df=1, 11$, $p<0.05$, Scheffé test), or placebo alone ($F=5.85$, $df=1, 9$, $p<0.05$, Scheffé test).

According to ratings available for follow-up on the Personal Report of Confidence as a Performer, all six of the available subjects given cognitive-behavior therapy with placebo improved, and five had good endpoint functioning. Four of the six available subjects given cognitive-behavior therapy with buspirone improved, and three had good endpoint functioning. Four of the seven subjects given buspirone without cognitive-behavior therapy improved, and three had good endpoint functioning. Three of the five subjects given placebo without cognitive-behavior therapy improved, and none had good endpoint functioning. The only significant findings for these measures were that more subjects given cognitive-behavior therapy with placebo than those given placebo alone improved ($\chi^2=5.0$, $df=1$, $p<0.05$) and had good endpoint functioning ($\chi^2=5.2$, $df=1$, $p<0.05$).

## DISCUSSION AND CONCLUSIONS

Performance anxiety had important consequences for these musicians: most of them reported some avoidance of performing. Three of the full-time professional musicians had stopped performing, suggesting that performance anxiety can cause occupational disability. As found in other studies, use of $\beta$ blockers was common among professional musicians (4, 5) but not among the nonprofessional musicians (7). The use of alcohol for relief of symptoms was also reported by many of the subjects.

The characteristics of this group were similar to those of groups with social phobia reported in the literature: their age at onset was when they were teenagers; there was an approximately equal number of men and women (29); they had similar scores on the Fear of Negative Evaluation Scale, the Social Avoidance and Distress Scale, and the State-Trait Anxiety Inventory (30); and they used alcohol as an anxiolytic in phobic situations (31). Many of these musicians had a history of major depression, also characteristic of patients with social phobia (32). These findings are consistent with categorizing performance anxiety in musicians as a form of social phobia. Further, they indicate that most musicians with performance anxiety do not have the generalized type of social phobia. Rather, similar responses to the speech and the musical performance, high scores on ratings of fear of negative evaluation, and correlations between anxiety and cognitive style suggest that this group is best characterized as having anxiety in performance situations in which an evaluation is explicit or implied.

The laboratory assessment demonstrated that these musicians experienced substantial physiological changes during performances, reflected by heart rate increases. Palpitations and tachycardia are frequently cited symptoms of anxiety in musicians (7), and the musicians in this study experienced substantial increases in heart rate during both the musical performance and the speech. Although the increases in heart rate and subjective anxiety were correlated for the speech, there was no corresponding correlation for the musical performance. Heart rate was also apparently not a sensitive indicator of change because improvement in anxiety was not reflected by a change in heart rate during performances following treatment. This lack of a correlation between heart rate and anxiety may have been due to the confounding influence of differences in exertion between performances. For example, wind instrumentalists might experience greater increases in heart rate due to exertion than guitarists. Other uncontrolled factors include the use of caffeine and cigarettes before arrival at the laboratory and differences in cardiovascular fitness.

Despite the relatively brief cognitive-behavior therapy intervention, subjects receiving this treatment showed statistically significant mean improvements on all major outcome variables. That significant change on the Personal Report of Confidence as a Performer occurred only at the follow-up assessment suggests that subjects learned useful skills in cognitive-behavior therapy but did not have the opportunity to practice them sufficiently during the 5-week program. Kendrick et al. (21) reported similar findings. Although this result is encouraging with regard to the effectiveness of cognitive-behavior therapy, one would hope for more clinically robust changes in both psychological and physiological measures. The lack of change in some areas may reflect inadequacies in the content and length of this cognitive-behavior therapy program. Many participants informally remarked that additional sessions would have been useful for additional exposure as well as for further discussion of cognitive strategies. A greater emphasis on cognitive strategies may be particularly important for professional musicians, for whom the exposure provided in this program may be less relevant. Furthermore, nonspecific treatment effects cannot be excluded as possibly contributing to improvement. Although placebo provided a blind control for medication assignment, it was not possible to blind patients to cognitive-behavior therapy assignment.

Buspirone was not found to result in statistically significant improvement on any measure. Although a few subjects took less than the recommended dose, eliminating these subjects from the analysis did not change the negative result. On the other hand, some measures showed more improvement with buspirone than with placebo, and the small sample may have provided inadequate power to detect differences. The statistically significant disadvantage of buspirone compared with placebo on change in the Self-Statement Questionnaire may have been a chance finding.

These questionnaire and assessment studies document that performance anxiety can be a serious disorder in some musicians, leading to occupational disability and other important consequences. The small sample size prevents any definitive statement regarding the usefulness of buspirone for performance anxiety. Although a study with a larger sample and a more extensive cognitive-behavior therapy program is needed, the results strongly suggest that cognitive-behavior therapy is a viable treatment approach for performance anxiety.

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## APPENDIX 1. Cognitive-Behavior Therapy Program Given to 17 Musicians With Performance Anxiety

### SESSION 1

Introduction and rationale for cognitive-behavior therapy
Self-statement analysis presented
Homework: List positive and negative self-statements

### SESSION 2

Techniques for modifying self-statements
Coping model 1 (slide and audiotape presentation)
Replay laboratory performance audiotapes and discuss negative and positive cognitions
Homework: Self-statement modification exercise

### SESSION 3

Coping model 2 (slide and audiotape presentation)
Applied relaxation training—long version
Exposure performances
Homework: Applied relaxation practice—long version and self-statement exercise

### SESSION 4

Applied relaxation training—short version
Exposure performances
Homework: Applied relaxation practice—short version and self-statement exercise

### SESSION 5

Exposure performance
Review and termination

# European Versus U.S. Data on the Course of Schizophrenia

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*Objective: The present research attempts to add to the existing body of data on the course of schizophrenia by comparing the findings of a prospective study of a group of U.S. schizophrenic patients with data from two European studies. Method: Seventy-four U.S. patients given the diagnosis of schizophrenia according to Research Diagnostic Criteria were longitudinally assessed at hospitalization and at three intervals up to 10 years after illness onset. The longitudinal criteria for type of onset, course of illness, and outcome were derived from the European studies of Manfred Bleuler and Luc Ciompi. The type of onset, course of illness, and outcome of the U.S. patients were compared with those of the patients in the two European studies. Results: A lower rate of acute onset and of episodic illness was found in the U.S. patients, but the relative frequency of a number of major overall course patterns was similar across studies. Conclusions: Despite many potential threats to comparability, the results of the European and U.S. longitudinal studies of the course of schizophrenia were fairly congruent in terms of the relative rate with which patients fell into the categories established by Bleuler and Ciompi. These results are encouraging in that they point to the possibility of estimating the rate of occurrence of particular expressions of the overall course of schizophrenia.*

(Am J Psychiatry 1991; 148:606–611)

Within the last two decades, major investigations in Europe and in non-Western countries have provided data on the longitudinal course and outcome of schizophrenia (1, 2). Ten studies conducted in North America that followed the course of schizophrenia for at least 10 years and used well-specified methodologies have been identified (3). These studies have produced information vital to our understanding of the course of schizophrenia over many years. However, variations in schizophrenia course criteria and classifications have limited systematic cross-study comparisons.

Manfred Bleuler (4) and Luc Ciompi (5, 6) specifically categorized the courses of schizophrenia found in their studies of European patients in terms of eight longitudinal patterns. Bleuler and Ciompi constructed these patterns by observing and combining three longitudinal features: illness onset, intervening course, and outcome. Bleuler and Ciompi reported the percentage of patients showing each of the patterns, along with the criteria for inclusion, allowing for cross-study comparison.

Using Bleuler and Ciompi's classifications, Harding (7) examined retrospectively the 32-year course of illness of a group of 82 U.S. patients given the diagnosis of schizophrenia according to *DSM-III.* Harding found a smaller percentage of U.S. patients with illness patterns characterized by an acute onset, episodic course, and mild or recovered outcome than did Bleuler and Ciompi. Harding also reported a larger percentage of patients who showed patterns of 1) chronic onset, episodic course, and mild or recovered outcome and 2) chronic onset, episodic course, and moderately severe outcome than did either Ciompi or Bleuler.

Disagreements across studies can be partially understood in terms of methodological differences in diagnosis, observational techniques, outcome cutoffs, and sampling (6, 7). For example, Harding's study was originally targeted to study the outcomes of long-stay patients later released to the community; this would lower the possibilities of observing patients with the pattern of acute onset and recovered outcome. Bleuler (4, p. 6), in turn, noted that his group of patients may have underrepresented those who remained hospital-

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ized after an initial episode and those who after discharge remained socially adapted, which would increase the representation of patients whose illness was episodic. Ciompi's retrospective observations were based on patients in older adulthood. Due to this design, Ciompi (5, p. 608) cautioned that specific course ratios may have been affected by the earlier death of many in his patient group.

Despite a host of potential threats to comparability, these studies are moderately congruent in terms of the relative rate with which patients fell into the categories defined. As we study more patients, the closer we may come to estimating the likelihood of the different courses schizophrenia may take.

The present research attempts to add to the existing body of data in this area by presenting the longitudinal courses found in a group of U.S. schizophrenic patients prospectively examined up to 10 years after the onset of illness. Efforts were made to conform to the criteria outlined in the European studies of Bleuler and Ciompi to make cross-study comparisons possible. Importantly, these data add a prospective view of schizophrenia assessed at multiple specified time points over the course of disorder.

## METHOD

### *The U.S. Study*

The subjects in the U.S. study were 74 patients from the Chicago Follow-Up Study (8–10). All subjects were diagnosed as having schizophrenia according to Research Diagnostic Criteria (RDC). These subjects represent a group of schizophrenic patients (excluding those who committed suicide and those who died) followed up three times at 2–3-year intervals after hospital discharge. RDC diagnoses were made by a diagnostic team blind to follow-up data and to the purpose of this specific study. The team used information gathered at the index hospitalization, including data from the Schedule for Affective Disorders and Schizophrenia (SADS) (11), the Schizophrenia State Inventory (10), research interviews, and hospital charts.

The 74 patients were relatively young at their first hospitalization (mean±SD age=20.8±3.5 years) and at the index hospitalization (22.9±3.9 years), our first observational point. Their mean age at the third follow-up, 8 years after the index hospitalization and 10 years after first hospitalization, was 31 years. The index hospitalization was the first admission for 29 (39%) of the 74 patients.

The U.S. study group was demographically diverse in gender (48 [65%] were men), race (53 [72%] were white), and social class (36 [49%] were middle-class or upper-class [12]). Intellectual functioning was within average ranges (WAIS information subscale estimate=10.6±3.0), 54 (73%) of the patients had completed high school or some college, and 54 (73%) had never married. Almost three-quarters of the subjects received neuroleptic medication during the follow-up period: 32 (43%) received it during all three follow-up intervals, 16 (22%) during two follow-up intervals, and seven (10%) during only one follow-up interval. Analyses of associations between neuroleptic use and course of schizophrenia will be presented in the Results section. However, caution should be applied in using these naturalistic study data to interpret the efficacy of medication because patients were not assigned to treatment condition on a random basis and compliance was not assessed.

### *The European Studies*

Bleuler's 208 subjects were admitted to Zurich Psychiatric University Clinic during 1942–1943 and were observed until 1964–1965 (approximately 23 years). They had a mean age at index admission of 40 years, 33% were first admissions, 48% were men, and 28% were married. They represented a range of social classes, although on average they came from a slightly lower socioeconomic strata than their corresponding community (4). Neuroleptics were in use during the last 9–10 years of Bleuler's study. Previous treatment included work therapy, sedatives, and a variety of somatic methods.

Ciompi's 289 subjects were derived from the University Psychiatric Clinic of Lausanne and were born between 1873 and 1897. The mean age at first hospitalization of the men was 33.2±10.6 years, and that of the women was 44.4±12 years. The mean follow-up duration was 36.9 years from first admission, and the subjects represented a predominantly rural and small-town population. Only 4% of Ciompi's subjects were treated with neuroleptics because most of these patients lived before the neuroleptic era.

The diagnosis of schizophrenia in both European studies followed the system of Eugen Bleuler and excluded the course of psychosis as a criterion. The diagnostic concept in the European studies is thus broader than *DSM-III* and includes schizophreniform disorder (as does the RDC diagnosis in the U.S. group). In addition, the European studies may have included some disorders classified by RDC and *DSM-III* as affective and schizoaffective psychoses (1).

### *Procedure*

The design of the U.S. study included extended evaluations during the index hospitalization. Information relevant to illness onset; frequency, duration, and nature of previous episodes; and premorbid adjustment were obtained at the index admission (9, 10).

Follow-up evaluations were done at 2–3-year intervals after discharge from the index hospitalization. These standardized assessments evaluated the occurrence of symptoms, hospitalization, treatment, and adjustment during each interval. Evaluations included

**TABLE 1. Frequency of Ciompi's Courses of Schizophrenia in Europe and the United States**

| | U.S. Study (N=74) | | Ciompi's Study (5) (N=228)[a] | |
|---|---|---|---|---|
| Course of Illness | N | % | N | % |
| Acute onset, undulating course, recovered or mild outcome | 8 | 10.8 | 58 | 25.4 |
| Acute onset, undulating course, moderately severe outcome | 7 | 9.5 | 27 | 11.8 |
| Acute onset, simple course, recovered or mild outcome | 5 | 6.8 | 12 | 5.3 |
| Acute onset, simple course, moderately severe outcome | 10 | 13.5 | 19 | 8.3 |
| Chronic onset, undulating course, recovered or mild outcome | 5 | 6.8 | 22 | 9.6 |
| Chronic onset, undulating course, moderately severe outcome | 9 | 12.2 | 12 | 5.3 |
| Chronic onset, simple course, recovered or mild outcome | 3 | 4.1 | 23 | 10.1 |
| Chronic onset, simple course, moderately severe outcome | 27 | 36.5 | 55 | 24.1 |

[a] In 61 cases, onset, course type, or outcome could not be determined with certainty (5, p. 612).

the SADS and/or a modified version of the Present State Examination (13), the Katz and Lyerly adjustment scales (14), and a comprehensive assessment of work, educational, social, hospitalization, and medication patterns (10). This information was used to rate the course of illness according to criteria derived from the work of Manfred Bleuler (4) and Ciompi (5, 6) (appendix 1).

Although criteria for illness onset, course, and outcome were made to conform to the European studies, the time frame of the U.S. outcome assessments was necessarily different. In the European studies, the outcome was defined as a plateau that an individual reached and maintained for at least 5 years. Bleuler's subjects had illness histories of 20 years or more. In contrast, our group of patients, to date, has been observed over a shorter period of time, and outcomes refer to the condition of each patient over the 2 years preceding the third follow-up. However, correlations among outcomes assessed at each of the three follow-ups showed significant stability over time (r values=0.63 to 0.77).

Unweighted kappa values (15) between two independent raters (J.M. and J.S.) showed fair to good agreement in assessments of illness onset (kappa=0.59), intervening course (kappa=0.60), outcome (kappa=0.71), and overall course (Bleuler criteria, kappa=0.41; Ciompi criteria, kappa=0.60). Consensus meetings were held to identify and resolve sources of discrepancy. The most common rating difficulties were in tracking the features and time frames of illness onset and in assessing the degree of recovery between illness episodes.

**TABLE 2. Frequency of Bleuler's Courses of Schizophrenia in Europe and the United States[a]**

| | U.S. Study (N=74) | | Bleuler's Study (4) (N=205) | |
|---|---|---|---|---|
| Course of Illness | N | % | N | % |
| Acute onset, undulating course, recovered | 12 | 16.2 | 45 | 22.0 |
| Acute onset, undulating course, mild or moderately severe outcome | 7 | 9.5 | 55 | 26.8 |
| Acute onset, undulating course, severe outcome | 1 | 1.4 | 19 | 9.3 |
| Acute onset, simple course, mild or moderately severe outcome | 7 | 9.5 | 4 | 2.0 |
| Acute onset, simple course, severe outcome | 2 | 2.7 | 2 | 1.0 |
| Chronic onset, simple course, mild or moderately severe outcome | 18 | 24.3 | 47 | 22.9 |
| Chronic onset, simple course, severe outcome | 12 | 16.2 | 25 | 12.2 |
| Atypical course | 15 | 20.3 | 8 | 3.9 |

[a] Undulating courses are episodic in that periodic episodes are followed by mild or remitted illness. Simple courses include moderately severe chronic psychosis without intervening remissions. Bleuler's typology differs from Ciompi's typology in that onset and course, although independently assessed, are combined in Bleuler's categorization. Three probands were listed as deceased (4, pp. 210, 267).

## RESULTS

### *The Overall Course of Illness*

Tables 1 and 2 contain the eight descriptions of overall course of illness developed by Ciompi and Bleuler and the occurrence rates of these courses across studies. A high rate of occurrence was found for courses characterized by 1) a chronic onset, simple course, and moderate-to-severe outcome and 2) an acute onset, undulating (episodic) course, and recovered or mild outcome. A low rate of occurrence was found across studies for courses characterized by an acute onset, simple course, and recovered or mild outcome.

Between-study discrepancies (defined as a difference of 10% or more in occurrence rate) were found in courses characterized by an acute onset, undulating course, and recovered or mild outcome (less frequent in the U.S. study than in Ciompi's) and by a chronic onset, simple course, and moderately severe outcome (more frequent in the U.S. study than in Ciompi's). A higher rate of atypical course and a lower rate of acute onset, undulating (episodic) course, and a mild or moderately severe outcome were seen in the U.S. group than in Bleuler's. In all studies, a severe outcome was less often associated with an acute onset than a chronic onset, and a chronic onset resulting in recovery was infrequent.

### *Acute and Chronic Illness Onset*

Bleuler (4) categorized "peracute," acute, and subacute illness onsets as "acute" and defined by a time frame of less than 3 months before the expression of the full syndrome (appendix 1). Of Bleuler's 208 patients, 129 (62%) had acute illness onsets and 79 (38%) had chronic illness onsets (4, p. 198). In contrast, using Bleuler's 3-month criterion, we found that only 23 (31%) of our 74 patients had acute onsets.

When we applied Ciompi's more liberal criterion (less than 6 months for acute onset) (5), the rates of acute and chronic illness onset in our group and Ciompi's were more similar: 30 (40.5%) of our patients and 50.9% of Ciompi's had acute onsets, and 44 (59.5%) of our patients and 49.1% of Ciompi's had chronic onsets. However, more of our patients had chronic onsets than did the patients in either European study. The type of onset was not significantly related to any of the demographic features assessed in this U.S. study. Across studies, acute onsets were less frequently associated with poor outcomes, and chronic onsets more frequently evolved into simple illness courses (tables 1 and 2).

### *Intervening Course Variations*

Occurrence rates for simple and episodic intervening courses showed some between-study variability. More of the patients in the European groups (52% in Ciompi's group and 58% in Bleuler's) than in the U.S. group (29 [39%] of the patients) had undulating (episodic) courses. Atypical course patterns, which usually reflected a combination of simple and episodic periods (without intervening remission), were more prominent in the U.S. patients (table 2).

In the U.S. group, comparisons between patients with episodic versus simple courses suggested that episodic illness was associated with higher educational levels ($t=2.01$, $df=54$, $p<0.05$) and with an intact marriage at follow-up ($\chi^2=9.00$, $df=2$, $p<0.02$). Age at first admission, gender, social class, race, and estimated IQ were not significantly associated with type of course. U.S. patients who did not receive neuroleptic medication over the follow-up period had significantly different course patterns from those who did receive neuroleptics during one or more follow-up intervals ($\chi^2=10.47$, $df=2$, $p<0.006$). Thirty-five (90%) of the 39 patients with simple courses reported neuroleptic use, although 12 (60%) of the 20 patients with episodic courses and eight (53%) of the 15 with atypical courses also reported receiving neuroleptic medication at some point during follow-up.

### *Outcome States*

Favorable versus unfavorable outcomes were similar across U.S. and European studies despite differences in the length of follow-up (table 3). Approximately 20%–27% of the patients in each group recovered, and about 20% of each group were severely impaired at the last evaluation. The remaining patients in both the U.S. and European groups were almost evenly divided between mild and moderately severe outcome states.

**TABLE 3. Outcome States of Patients With Schizophrenia in One U.S. and Two European Studies**

| | U.S. Study (N=74) | | Ciompi's Study (N=289) | | Bleuler's Study (N=208) | |
|---|---|---|---|---|---|---|
| Outcome | N | % | N | % | N | % |
| Recovered | 17 | 23.0 | 77 | 26.6 | 41 | 19.7 |
| Mild | 21 | 28.4 | 64 | 22.1 | 67 | 32.2 |
| Moderately severe | 21 | 28.4 | 69 | 23.9 | 41 | 19.7 |
| Severe | 15 | 20.3 | 52 | 18.0 | 43 | 20.7 |
| Uncertain | — | — | 27 | 9.3 | 16 | 7.7 |

## DISCUSSION

This research compared the distribution of courses of schizophrenia diagnosed according to RDC found in a prospective, longitudinal U.S. study with those found in two European studies. The European studies were conducted by Manfred Bleuler and Luc Ciompi, whose criteria and course distributions were most accessible based on the available publications.

Cross-study comparisons indicate some similarity in rates of overall course of schizophrenia. One common course found across studies (and most frequent in the U.S. group) was characterized by a chronic onset, simple (nonepisodic) intervening course, and moderately severe outcome. Another common course was characterized by an acute onset, episodic course, and recovered or mild outcome.

Simple courses occurred more frequently in the U.S. group than in the European studies, which reported a greater rate of episodic illness. Factors that may account for this discrepancy are 1) the shorter assessment period in the U.S. study (10 years) than in the European studies (20 or more years) (i.e., future episodes may yet occur) and 2) sampling and diagnostic factors (the U.S. RDC diagnoses excluded affective psychoses). Neuroleptic use was commonly (but not exclusively) associated with a simple course in the U.S. group and may be related to a restriction of illness episodes. However, this study involved patient self-report regarding medication use, and treatment compliance was not assessed. Bleuler and Ciompi used patients primarily representative of a preneuroleptic era, so they did not report associations between illness course and medication use.

Outcome rates were similar across U.S. and European studies and in line with expectations (i.e., approximately one-fifth of the group showed recovered or mild outcomes, one-fifth showed very severe impairment, and the remaining three-fifths showed intermediate outcomes). Although the U.S. group had a higher rate of chronic (insidious) illness onset than was found in Bleuler's study, this difference lessened when Ciompi's 6-month criterion was used to demarcate acute illness onset from chronic onset. Bleuler (4) expressed the frustration that concepts such as onset, outcome, and intervening course were not well defined. The time frames for illness onset were among the most problematic assessments in the U.S. study group and showed the greatest deviation from European rates.

Carpenter and Kirkpatrick (16) raised a potential limitation in using the eight categories of illness course presented in the European studies. These investigators noted that many symptom and adjustment factors must be condensed to create the dichotomies involved in the eight-course schema (i.e., acute versus chronic onset, simple versus episodic course, good versus poor outcome). Carpenter and Kirkpatrick pointed out that it also may be useful independently to assess, dichotomize, and study the course relationships of specific psychotic and nonpsychotic illness features (i.e., positive symptoms, negative symptoms, cognitive and attentional disturbances, etc.) over time. Their point is well-taken. However, in the interest of comparing the courses of our patients with those of the patients of Bleuler and Ciompi, we used existing typologies and a syndromal approach.

Although increased methodological standardization is needed, documenting the longitudinal courses of illness and the features of these courses remains important to our understanding of schizophrenia. Empirically, this documentation can help to identify contributors to course heterogeneity and aid in the construction of more accurate prognostic models. Clinically, it may enrich evaluations of treatment effectiveness, improve communication among clinical care agencies, and enhance information provided to patients and their families. The data reported here emphasize a number of cross-nation similarities in the course of schizophrenia, pointing to the encouraging possibility of estimating the rates of occurrence of particular expressions of the overall course of schizophrenia.

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## APPENDIX 1. Criteria for Onset, Course, and Outcome of Schizophrenia According to Manfred Bleuler and Luc Ciompi

### CRITERIA FOR ILLNESS ONSET

*Bleuler*

1. *Acute.* "Whenever the illness or phase of illness developed within a few days (peracute) or weeks (acute), or at the outside within a few months (subacute) . . . personality changes that are not unequivocally psychotic are disregarded . . . an onset of illness is considered . . . when the patient first expresses delusions or hallucinations, when he begins to talk in such confusion that he is regarded as mentally ill by people around him, when he begins to neglect his customary duties for no apparent reason, when he ceases to talk, refuses to eat, when he rants, etc." (4, pp. 190, 198).

2. *Chronic.* "If it is not possible to determine the onset of illness as having developed within the period of a few weeks or in a very few months, but the illness develops almost unnoticed over the course of several months, I assume a chronic onset" (4, p. 190).

*Ciompi*

1. *Acute.* "Less than six months from appearance of the first symptoms to a complete picture of a psychosis" (5, p. 610).

2. *Chronic.* "More than six months from the appearance of first symptoms to a complete picture of a psychosis" (5, p. 610).

### CRITERIA FOR INTERVENING COURSE

*Bleuler and Ciompi*

1. *Undulating.* "The periods of illness that begin acutely and recede acutely I refer to as acute phases or undulations of a schizophrenic psychosis. They may involve a first time or a repeated phase of illness. They may develop from a normal state of health or from a milder chronic condition, and then again they may revert to a recovery or to a milder chronic state. To qualify as an undulation, a phase must have lasted at least a week. Excitations of short duration . . . were not counted as undulations . . . nor did we consider it an undu-

lating phase of illness . . . when a severe depressive or stuporous condition passed over into a severe manic-like state or one of extreme excitation" (4, p. 192).

2. *Simple.* Long-term but stable chronic psychosis (4, p. 209). In the U.S. study, simple courses reflected continuing moderately severe levels of psychosis without symptom episodes or remissions.

3. *Atypical.* "Those courses that are clear and yet cannot be put into one of the above categories for one reason or another. The most common among them are acute exacerbations that develop after a long-term chronic course" (4, p. 211).

## CRITERIA FOR OUTCOME

### *Bleuler and Ciompi*

1. *Recovery.* Complete recovery or those who suffer only residual impairment; ancillary symptoms (mild to severe); possible residues of delusional ideas or faulty perception; functioning well in other areas of assessment; resumes former role in society and in the family; not considered mentally ill by others—although may be considered odd or eccentric; fully employed in gainful work.

2. *Mild.* Able to maintain sensible conversation except when discussing topics that concern psychotic experiences; overt behavior is generally normal (illness not immediately obvious); able to work and working, although it may be at a lower level than before the onset.

3. *Moderately severe.* Similar to severe, but moments when patient breaks out of more severe state (fluctuations are seen); also, those who can communicate adequately but who constantly reveal thought disturbances, even when speaking of impersonal topics; work performance lower than before illness.

4. *Severe.* Constant care and supervision required (can be at home, in a halfway house, or in a hospital); appears to be indifferent to human contact and/or environment; never carries on coherent, comprehensible conversation: mutistic or speaks in great confusion; usually no work, but at best purely mechanical tasks.

# A Family Study of *DSM-III-R* Schizoaffective Disorder, Depressive Type, Compared With Schizophrenia and Psychotic and Nonpsychotic Major Depression

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*Objective: To assess the validity of* DSM-III-R *schizoaffective disorder, the authors explored the morbid risks for schizophrenia and major affective disorders in the first-degree relatives of patients with schizoaffective disorder and relevant other diagnoses. Method: In addition to patients with* DSM-III-R *schizoaffective disorder, depressive type (N=21), the probands included patients with mood-incongruent psychotic depression (N=22), mood-congruent psychotic depression (N=19), nonpsychotic depression (N=27), or schizophrenia (N=28) and normal subjects (N=18). The patients were consecutively recruited from the outpatient facilities of a university psychiatry department; the normal subjects were students and nurses. All probands were directly interviewed, with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L), by a psychiatrist blind to information about relatives. Consenting relatives were directly interviewed, with the SADS-L, by two psychiatrists blind to the probands' diagnoses. The direct interview was supplemented—or replaced, when an interview was not possible (24%)—by family history data from all available sources. Morbid risks in relatives were calculated according to the Weinberg method. Results: The relatives of the schizoaffective patients had almost the same risk for schizophrenia as the relatives of the schizophrenic patients. In the relatives of the patients with mood-incongruent psychotic depression, the morbid risk for major affective disorders was about one-half that of the relatives of the patients with mood-congruent psychotic depression and one-third that of the relatives of the patients with nonpsychotic depression, but these differences did not reach statistical significance. Conclusions: These results suggest that* DSM-III-R *schizoaffective disorder is close to schizophrenia and largely corresponds to mainly schizophrenic schizoaffective disorder in the Research Diagnostic Criteria, whereas* DSM-III-R *mood-incongruent psychotic depression is probably quite heterogeneous and should be studied further.*

(Am J Psychiatry 1991; 148:612–616)

The heterogeneity of schizoaffective disorders, when they are generically defined as "episodic disorders in which affective and schizophrenic symptoms are both prominent and present simultaneously" (*ICD-10*, 1990 draft), has been repeatedly documented by studies focusing on family history (1, 2), long-term course and outcome (3, 4), and response to drug treatment (5, 6). This heterogeneity has been found to be more pronounced in the unipolar schizodepressive form (7, 8), whereas bipolar schizoaffective disorder more consistently resembles "pure" bipolar affective disorder in outcome and response to drug treatment (4, 9, 10).

The first step in the identification of more homogeneous types of schizoaffective disorder was the development of the Research Diagnostic Criteria (RDC) (11), in which "mainly affective" and "mainly schizophrenic" types were identified. The type is based on the temporal relationship between the occurrence of the affective and the schizophrenic-like symptoms and on the quality of the premorbid adjustment. The validity of this dichotomy has been supported by family (12) and drug response (6) studies, but the data provided by outcome studies have been less clear; some investigations have confirmed the validity of the dichotomy (13, 14), and others have shown no significant difference between patients with mainly affective and mainly

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schizophrenic schizoaffective disorder (15–17). (Not relevant to the issue are studies [e.g., 18] in which schizoaffective patients were divided into "affect-dominant" and "schizo-dominant" on the basis of criteria very different from the RDC. Those criteria cover "sequential" schizoaffective disorder [19], in which affective and schizophrenic syndromes occur in different episodes, in addition to "concurrent" schizoaffective disorder [the only type included in the RDC].)

The RDC dichotomy of the mainly affective and the mainly schizophrenic types of schizoaffective disorder has been substantially revived in *DSM-III-R*. In fact, the *DSM-III-R* category of schizoaffective disorder largely overlaps the RDC mainly schizophrenic type of schizoaffective disorder, since the crucial criterion for the diagnosis of the former condition ("during an episode of the disturbance, there have been delusions or hallucinations for at least two weeks, but no prominent mood symptoms") is almost exactly the same as one of the two alternative criteria defining the latter ("core schizophrenic symptoms were present for at least 1 week in the absence of manic or depressive features"). On the other hand, the *DSM-III-R* categories of mania and major depression with mood-incongruent psychotic features resemble the RDC mainly affective type of schizoaffective disorder, since they share with this condition two essential features: 1) the presence of a manic or major depressive syndrome accompanied by psychotic symptoms that are not "typical" of affective disorders and 2) the occurrence of psychotic symptoms only during times when the patient has prominent mood symptoms.

The validation of the *DSM-III-R* category of schizoaffective disorder is still in a preliminary phase: specifically, to our knowledge, no family study on patients suffering from this condition has been published as yet. In the present paper we report on the morbid risks for schizophrenia and for major affective disorders of first-degree relatives of patients with a *DSM-III-R* diagnosis of schizoaffective disorder, depressive type, patients with schizophrenia, patients with different types of major depression, and normal subjects. We chose to focus on the depressive rather than the bipolar type of *DSM-III-R* schizoaffective disorder because we have found that the former is much more frequent (at least five times as prevalent, according to our experience).

## METHOD

The study was carried out with the following proband groups: 1) 21 patients with a *DSM-III-R* diagnosis of schizoaffective disorder, depressive type (nine men and 12 women, aged 24–46 years), 2) 22 patients suffering from *DSM-III-R* major depression (either single episode or recurrent) with mood-incongruent psychotic features (eight men and 14 women, aged 27–49 years), 3) 19 patients suffering from *DSM-III-R* major depression with mood-congruent psychotic features (seven men and 12 women, aged 28–51 years), 4) 27 patients suffering from *DSM-III-R* major depression, severe, without psychotic features (10 men and 17 women, aged 27–51 years), 5) 28 patients with a *DSM-III-R* diagnosis of schizophrenia (13 men and 15 women, aged 21–43 years), and 6) 18 subjects with no personal history of psychiatric disorders (eight men and 10 women, aged 21–49 years). The patients with schizoaffective disorder were recruited from consecutive patients in the outpatient facilities of a university psychiatry department. The patients with other diagnoses were recruited from consecutive patients in the same outpatient facilities but were selected on the basis of suitability for sex and age matching to the schizoaffective patients already enrolled (we allowed ±5 years for age matching). The normal subjects were students and nurses, recruited so as to obtain a sex ratio and an age distribution similar to those of the patients with schizoaffective disorder. All probands were directly interviewed by means of the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (20). All of the interviews were conducted by the same psychiatrist, who was blind to information about the probands' relatives.

Consenting first-degree relatives were directly interviewed, with the SADS-L, by two psychiatrists, who were blind to the probands' diagnoses. The direct interview was supplemented—or replaced, when an interview was not possible (24% of the cases)—by family history data from all available sources (other family members, health care providers, medical records). The information concerning each relative was reviewed by an independent clinician, who assigned a "best estimate" diagnosis according to *DSM-III-R* criteria. The proportion of relatives who could not be directly interviewed was almost the same in the six proband groups. Moreover, these groups did not differ significantly with respect to the distribution of relative types (parents, siblings, and offspring).

The morbid risks for schizophrenia and for major affective disorders in the relatives of the probands in each group were calculated by means of the abridged Weinberg method (21), which weights each relative's risk according to the proportion of the risk period through which he or she has passed. We chose this method of age correction, rather than the original Strömgren method (22), because of the difficulty of establishing the exact onset of the first episode, which seldom coincided with the period of first treatment, in the relatives. According to Larsson and Sjögren (23), the use of the Weinberg method is justified provided that mortality in the relatives does not show any remarkable irregularity (in our subjects no irregularity was observed). The risk periods we used were ages 15–50 years for schizophrenia and ages 15–70 years for major affective disorders, as suggested by Perris (24).

The statistical comparison of the morbid risks of the relative groups was performed with the u test for the assessment of differences between two proportions

**TABLE 1. Morbid Risk for Schizophrenia and Major Affective Disorders in First-Degree Relatives of Patients With *DSM-III-R* Schizoaffective Disorder, Major Depression, or Schizophrenia and of Normal Subjects**

| | Morbid Risk in Relatives | | | |
|---|---|---|---|---|
| | Schizophrenia | | Major Affective Disorders | |
| Proband Group | N[a] | Morbid Risk (%)[b] | N[a] | Morbid Risk (%)[c] |
| Schizoaffective disorder, depressive type (N=21) | 46 | 8.7 | 42 | 2.4 |
| Major depression | | | | |
| Mood-incongruent psychotic (N=22) | 52 | 3.8 | 46 | 6.5 |
| Mood-congruent psychotic (N=19) | 45 | 2.2 | 41 | 12.3 |
| Nonpsychotic (N=27) | 65 | 0.0 | 59 | 16.9 |
| Schizophrenia (N=28) | 68 | 8.8 | 59 | 1.7 |
| Normal subjects (N=18) | 43 | 0.0 | 38 | 2.6 |

[a] Adjusted for period at risk.

[b] The following differences were significant: schizoaffective disorder versus nonpsychotic depression ($p<0.05$), schizoaffective disorder versus normal subjects ($p<0.05$), nonpsychotic depression versus schizophrenia ($p<0.01$), and schizophrenia versus normal subjects ($p<0.05$).

[c] The following differences were significant: schizoaffective disorder versus nonpsychotic depression ($p<0.05$), mood-congruent psychotic depression versus schizophrenia ($p<0.05$), nonpsychotic depression versus schizophrenia ($p<0.01$), and nonpsychotic depression versus normal subjects ($p<0.05$).

(25), as modified for use with morbid risk estimates (26).

## RESULTS

As shown in table 1, the first-degree relatives of the patients with *DSM-III-R* schizoaffective disorder, depressive type, had almost the same morbid risk for schizophrenia as the relatives of the schizophrenic patients, and they significantly differed in this respect from the relatives of both the patients with nonpsychotic depression ($u=2.42$, $p<0.05$, two-tailed) and the normal subjects ($u=2.00$, $p<0.05$, two-tailed). Moreover, they had a significantly lower morbid risk for major affective disorders than the relatives of the patients with nonpsychotic depression ($u=2.30$, $p<0.05$, two-tailed).

Further significant differences were the following: a significantly higher morbid risk for schizophrenia in the relatives of the schizophrenic patients than in the relatives of the patients with nonpsychotic depression ($u=2.68$, $p<0.01$, two-tailed) or the normal subjects ($u=2.20$, $p<0.05$, two-tailed), a significantly higher morbid risk for major affective disorders in the relatives of the patients with nonpsychotic depression than in the relatives of the schizophrenic patients ($u=2.79$, $p<0.01$, two-tailed) or the normal subjects ($u=2.18$, $p<0.05$, two-tailed), and a significantly higher morbid risk for major affective disorders in the relatives of the patients with mood-congruent psychotic depression than in the relatives of the schizophrenic patients ($u=2.20$, $p<0.05$, two-tailed).

In the relatives of the patients with mood-incongruent psychotic depression, the morbid risk for major affective disorders was about one-half that of the relatives of the patients with mood-congruent psychotic depression and one-third that of the relatives of the patients with nonpsychotic depression, but these differences did not reach statistical significance.

## DISCUSSION

The results of the present study suggest that schizoaffective disorder, as defined in *DSM-III-R*, is quite close to schizophrenia from the viewpoint of family history. It is important to stress that this finding has been obtained with patients whose schizoaffective disorder is unipolar, so it cannot be generalized to patients with the bipolar form of *DSM-III-R* schizoaffective disorder. It must also be added, however, that, according to our experience, the *DSM-III-R* criteria for schizoaffective disorder are rarely fulfilled by patients with a current manic syndrome or with a history of mania.

By and large, these results confirm the correspondence of *DSM-III-R* schizoaffective disorder to RDC schizoaffective disorder, mainly schizophrenic. Actually, the similarity between our *DSM-III-R* schizoaffective and schizophrenic patients with respect to family history pattern was even more marked than the similarity observed by Baron et al. (12) between patients with RDC mainly schizophrenic schizoaffective disorder and those with schizophrenia. This may reflect the greater specificity of the *DSM-III-R* criteria for schizoaffective disorder, in which the previous occurrence of florid psychotic symptoms (delusions or hallucinations) in the absence of prominent mood symptoms is mandatory, whereas the RDC category of mainly schizophrenic schizoaffective disorder also includes patients who exhibited, before the onset of affective symptoms, such features as social withdrawal, impairment in occupational functions, eccentric behavior, and unusual thoughts or perceptual experiences. These last patients resemble those described by Akiskal and Puzantian (27), in whom a manic or depressive syndrome is superimposed on the substrate of a schizotypal personality; the presence during acute episodes of peculiarities and oddities of ideation, perception, and behavior may prompt a diagnosis of schizoaffective disorder, and their persistence after recovery may be interpreted as residual schizophrenic symptoms. Such cases are not likely to be frequent in groups of patients with *DSM-III-R* schizoaffective disorder.

The notion that *DSM-III-R* schizoaffective disorder corresponds to RDC mainly schizophrenic schizoaffective disorder may have important practical implications. In particular, it may be predicted that patients with *DSM-III-R* schizoaffective disorder will respond poorly to lithium prophylaxis (6) and will benefit from long-term neuroleptic treatment (28). These assumptions, however, require direct support by empirical evidence.

Our findings concerning patients with a *DSM-III-R* diagnosis of major depression with mood-incongruent psychotic features may be relevant to the current debate about the proper nosological position of this condition (K.S. Kendler, paper commissioned by the DSM-IV Work Group on Psychotic Disorders). Although not statistically significant, the difference in the morbid risk for major affective disorders between the relatives of these patients and the depressed patients with mood-congruent psychotic features or without psychotic features was striking and argues against Pope and Lipinski's belief (29) that mood-incongruent delusions and hallucinations in the presence of a full affective syndrome are without importance from a family history perspective. These results are in line with those reported by Coryell et al. (30, 31) for patients with a *DSM-III* diagnosis of major depression with mood-incongruent psychotic features, but they are not consistent with those obtained by Baron et al. (12) for patients with RDC mainly affective schizoaffective disorder (in the relatives of these patients, the morbid risk for major affective disorders was almost the same as that of the relatives of patients with RDC major depressive disorder). This last discrepancy may in part reflect the fact that *DSM-III-R* major depression with mood-incongruent psychotic features, although resembling RDC mainly affective schizoaffective disorder in some important ways, also differs from it in other respects (in particular, a "good premorbid social and occupational adjustment" is required for the latter diagnosis but not for the former).

The relatively small size of the proband groups may somewhat limit the generalizability of the results of the present investigation. Nevertheless, the study is to our knowledge the first attempt to validate the *DSM-III-R* approach to the classification of mixed psychotic syndromes, which apparently reproduces the dichotomous model first proposed in the RDC. From the viewpoint of family history, it is clear the *DSM-III-R* schizoaffective disorder largely corresponds to RDC mainly schizophrenic schizoaffective disorder, since it is very close to schizophrenia. The position of *DSM-III-R* major depression with mood-incongruent psychotic features is less definite, and probably patients in this category are quite heterogeneous.

Further studies with larger groups of patients suffering from *DSM-III-R* major depression with mood-incongruent psychotic features are clearly needed. In these studies, it would be advisable to avoid pooling these patients with those suffering from *DSM-III-R* bipolar disorder with mood-incongruent psychotic features, since it may be expected that the family history patterns of the two groups are different.

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# Cortical Magnetic Resonance Imaging Changes in Elderly Inpatients With Major Depression

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*Objective: The purpose of the study was to determine if magnetic resonance imaging (MRI) scans of elderly depressed patients differ from MRI scans of age-matched control subjects and age-matched patients with Alzheimer's disease. Method: The authors studied 21 patients 60 years or older with major depression, 16 patients with Alzheimer's disease, and 14 age-matched control subjects. Results: Compared to control subjects, depressed patients had greater cerebral sulcal and temporal sulcal atrophy; larger sylvian fissures, lateral ventricles, third ventricles, and temporal horns; and greater severity of subcortical white matter lesions. Depressed patients also had more basal ganglia lesions but similar levels of periventricular hyperintensity. There were no differences between depressed patients with and without delusions on any MRI measure. Depressed patients who received ECT had more temporal horn atrophy and greater subcortical abnormality summary scores than normal subjects. Cortical sulcal atrophy correlated with age at onset of depression. Conclusions: The findings suggest that elderly hospitalized depressed patients have greater cortical as well as subcortical atrophy and more basal ganglia lesions than age-matched normal control subjects. The correlation of these abnormalities with outcome remains unknown.*

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Structural brain changes in depressed subjects of all ages have been reported for more than a decade (1–5). In the elderly, ventricle enlargement is linked to higher mortality rates (6) and is correlated with lower CT scan attenuation numbers (7). Recent studies by Coffey and associates (8–10) demonstrate subcortical white and gray matter changes on magnetic resonance imaging (MRI) scans of neurologically normal and neurologically impaired elderly depressed patients scheduled to undergo ECT. Similar white matter changes have been reported in young patients with bipolar disorder (11, 12); in those studies the MRI abnormalities were not associated with cognitive impairment.

We (5) have linked changes on CT scans to cognitive performance in elderly depressed patients. Older patients with the dementia syndrome of depression (13) had larger ventricle-to-brain ratio and lower regional residual CT attenuation numbers than age-matched normal subjects. Short-term follow-up of that sample (5) demonstrated that most of the older patients with the dementia syndrome of depression did not develop progressive dementia. These results suggested to us that poor cognitive performance in depression results, at least in part, from structural and functional brain changes rather than solely from poor attention or concentration.

Brain CT and MRI studies of depression to date have focused on subcortical changes. To determine whether elderly depressed patients have changes in cortical gray matter on MRI, to assess whether MRI changes are seen in older patients not undergoing ECT, and to clarify whether the previously described changes are distinct from changes seen in Alzheimer's disease (14, 15), we compared MRI scans of elderly depressed patients to those of age-matched normal subjects and patients with Alzheimer's disease.

## METHOD

MRI scans of 21 individuals with major depression, 16 patients with Alzheimer's disease, and 14 age-matched normal subjects were compared. The depressed patients were hospitalized on the inpatient psychiatric service of the Johns Hopkins Hospital and met *DSM-III-R* criteria for major depression. They had no history or evidence on physical examination of neurologic disease (e.g., stroke, Parkinson's disease), had no

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**TABLE 1. Ratings of Cortical and Subcortical MRI Changes in Elderly Normal Subjects, Depressed Patients, and Patients With Alzheimer's Disease**

| Measure | Normal Control Subjects (N=14) |  | Depressed Patients (N=21) |  | Patients With Alzheimer's Disease (N=16) |  | F (df=2, 47) | p | Difference From Normal Subjects (p)[a] |  |
|---|---|---|---|---|---|---|---|---|---|---|
|  | Mean | SD | Mean | SD | Mean | SD |  |  | Depressed Patients | Patients With Alzheimer's Disease |
| Cortical |  |  |  |  |  |  |  |  |  |  |
| Summary score | 2.37 | 1.32 | 4.90 | 1.60 | 5.20 | 1.65 | 15.00 | 0.0001 | <0.05 | <0.05 |
| Sylvian fissure | 0.76 | 0.66 | 1.93 | 0.76 | 1.85 | 0.78 | 12.05 | 0.0001 | <0.01 | <0.01 |
| Temporal sulci | 0.49 | 0.62 | 1.38 | 0.63 | 1.60 | 0.84 | 10.15 | 0.0002 | <0.01 | <0.01 |
| Cerebral sulci | 1.20 | 0.21 | 1.59 | 0.58 | 1.75 | 0.55 | 4.26 | 0.02 | <0.05 | <0.05 |
| Subcortical |  |  |  |  |  |  |  |  |  |  |
| Summary score | 2.74 | 1.87 | 6.44 | 4.39 | 7.86 | 3.66 | 7.37 | 0.002 | <0.05 | <0.05 |
| Third ventricle | 0.26 | 0.40 | 1.14 | 0.91 | 1.38 | 0.83 | 8.62 | 0.0006 | <0.01 | <0.01 |
| Temporal horns | 0.78 | 0.56 | 1.52 | 0.83 | 2.04 | 1.05 | 8.20 | 0.0009 | <0.05 | <0.01 |
| Lateral ventricles | 0.50 | 0.62 | 1.25 | 0.92 | 1.56 | 0.84 | 6.49 | 0.003 | <0.05 | <0.01 |
| Basal ganglia lesions | 0.14 | 0.36 | 0.65 | 0.67 | 0.50 | 0.30 | 3.11 | 0.05 | <0.05 | n.s. |
| White matter lesions | 0.50 | 0.51 | 0.90 | 0.89 | 1.10 | 0.50 | 3.10 | 0.05 | <0.05 | <0.01 |
| Periventricular hyperintensity | 0.69 | 1.03 | 1.05 | 1.24 | 1.31 | 1.01 | 1.10 | 0.34 | n.s. | n.s. |

[a] Post hoc comparisons by Duncan's test.

history of head trauma with loss of consciousness for more than 1 minute, and had a discharge Mini-Mental State examination (16) score greater than 23. The normal subjects were recruited by advertisement. They met none of the exclusionary criteria and had no past or current psychiatric history. The subjects with Alzheimer's disease were recruited from the Johns Hopkins Dementia Research Clinic. All met the criteria of the National Institute of Neurological Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association for possible or probable Alzheimer's disease (17).

MRI scans were performed on a single 1.5 Tesla General Electric scanner located in the neuroradiology department of the Johns Hopkins Hospital. Settings were as follows: repetition time (TR)=3000 msec and echo time (TE)=30/100 msec for 17 patients and TR=2500 msec, TE=20/80 msec for 34 patients. The MRI scans were rated according to the MRI rating draft of December 1989 of the Consortium for Establishing a Registry for Alzheimer's Disease (18). This protocol provides pictures of mild, moderate, or severe changes of the following structures on MRI scans: cerebral sulci, temporal lobe sulci, temporal horns, sylvian fissures, lateral ventricles, and third ventricle. Basal ganglia and cerebellar infarcts are counted and rated as 1–4, 5–9, or 10 and greater. Degree of periventricular hyperintensity and extent of subcortical white matter changes (white matter hyperintensities) are rated on 4-point scales from photographic examples of each stage. The periventricular hyperintensity and white matter hyperintensity ratings use both word and picture descriptors and are similar to those previously reported by Coffey et al. (8–10) and Fazekas et al. (19). If the verbal and photographic ratings differed, the picture rating was used. Because many scans fell between ratings, plus and minus ratings were added. For example, a scan that fell between ratings 1 and 2 would be rated as either "1+" (1.33) or "2−" (1.66) depending on which picture the scan in question appeared closer to.

MRI scans were rated by individuals who were blind to diagnosis and other clinical data. Three raters (P.V.R., G.D.P., and E.A.) concurrently evaluated each scan. If there was disagreement, a consensus rating was reached under the guidance of A.J.K., a neuroradiologist member of the instrument development team of the Consortium for Establishing a Registry for Alzheimer's Disease. Interrater reliability was determined by calculating the interclass correlation coefficient (ICC=0.85, F=1.73, df=62, 108, $p<0.01$). Summary scores of cortical and subcortical changes were calculated by adding the three cortical measures (cerebral sulci, temporal sulci, and sylvian fissures) and the six subcortical measures (lateral ventricles, third ventricle, temporal horns, periventricular hyperintensity, white matter hyperintensities, and basal ganglia/thalamus lesions).

The following data were collected on each subject: age, sex, race, median blood pressure (of five consecutive measures), and history of hypertension or cardiovascular disease. Groups were compared by using analysis of variance with Duncan's test to assess for post hoc comparisons.

## RESULTS

The three groups were similar in age (F=0.22, df=2, 48, p=0.80), race ($\chi^2$=1.72, df=2, p=0.42), and sex ($\chi^2$=4.70, df=2, p=0.10). Normal subjects were more likely to be scanned at the TR=2500 msec setting ($\chi^2$=21.7, df=2, $p<0.001$).

As table 1 shows, the depressed patients and patients with Alzheimer's disease differed from the normal subjects on all MRI measures except number of basal ganglia lesions and periventricular hyperintensity; only patients with Alzheimer's disease did not differ significantly from normal subjects on basal ganglia lesions. The depressed patients and patients with Alzheimer's disease differed from the normal subjects on both the cortical and subcortical summary measures. There were no differences between the depressed patients and patients with Alzheimer's disease on any measure.

Within the depressed group there were no differences between patients who subsequently underwent ECT (N=12) and those who did not (N=9) on any MRI measure except temporal horn rating (F=4.54, df=1, 19, p=0.05), which revealed more atrophy in patients who later received ECT. F ranged from 2.67 to 0.09, and p ranged from 0.16 to 0.77 on the other measures. Compared to depressed patients who received ECT, depressed subjects who did not receive ECT had lower subcortical summary scores (F=5.89, df=1, 19, p=0.03) but similar control summary scores (F=1.25, df=1, 19, p=0.28). There were no differences between depressed patients with delusions (N=7) and those without delusions (N=13) on any MRI measure (F ranged from 0.67 to 0.01, and p ranged from 0.46 to 0.92). (In one case the examiner was unable to discern the presence or absence of delusions.)

Admission Mini-Mental State scores for all subjects correlated inversely with the cortical summary measure ($r=-0.39$, N=51, $p<0.01$) and the subcortical summary measure ($r=-0.44$, N=51, $p<0.001$). Age at onset of depression correlated positively with degree of cortical sulcal enlargement ($r=0.80$, N=14, $p<0.01$) but with no other MRI measure. This correlation remained significant ($r=0.65$, N=14, $p<0.05$) after covariance by partial correlation analysis to remove the correlations between age and sulcal enlargement and between current age and age at onset. Within the depressed group there was no relationship between current median blood pressure and white matter hyperintensities (systolic blood pressure versus white matter hyperintensities: $r=0.03$, N=21, n.s.; diastolic blood pressure versus white matter hyperintensities: $r=-0.21$, N=21, n.s.) or between a history of ever having been treated for hypertension and severity of white matter hyperintensities (F=0.84, df=1, 19, p=0.37).

## DISCUSSION

To our knowledge this is the first report of MRI changes of cortical brain structure in elderly depressed patients. This extends the previous reports of subcortical abnormalities (8–10) and suggests that brain changes associated with depression in the elderly are diffuse and not limited to white matter hyperintensities or periventricular hyperintensity. The finding of cortical changes in elderly depressed patients not undergoing ECT also suggests that the cortical changes are present across the spectrum of depression severity.

The correlations between admission Mini-Mental State scores and the cortical and subcortical summary scores confirm our previous work showing a relationship between cognitive disorder and CT scan changes in depressed patients (5). The demonstration that the MRI changes are both cortical and subcortical is compatible with the hypothesis that a diffuse brain process is responsible. Vascular disease is one possible cause, as is an acceleration of whatever process underlies the changes seen on MRI in normal elderly subjects (20). However, since similar subcortical changes are reported in younger patients with bipolar disorder (11, 12) and elderly patients with major depression (10), it is plausible that some other diffuse process either causes or results from affective disorder. Examples could include the blood flow changes associated with affective disorder (21) or the effects of treatment.

The finding that age at onset is unrelated to the degree of subcortical change in spite of the wide range of age at onset (mean±SD=54.2±17.1 years, median=55.0, minimum age=23, maximum age=79) further suggests that these MRI changes are related to the presence of affective disorder and not primarily due to the elderly age of the sample. The recent reports of Dupont et al. (11, 12) demonstrating similar changes in younger patients with bipolar affective disorder support this contention. However, the correlation between sulcal atrophy and late age at onset suggests that a subset of patients with late-onset depression might be presenting with depression as a first manifestation of a cortical degenerative disorder such as Alzheimer's disease. Follow-up studies would be necessary to test this hypothesis.

While Tomlinson et al. (22) did not find any brain abnormalities in a neuropathologic examination of seven depressed elderly subjects, Bowen et al. (23), using both morphometric and neurochemical analyses, have demonstrated cell loss in the pars opicularis and temporal poles of elderly depressed patients. They also found selective serotonin 1A receptor loss in these regions and a generalized loss of serotonin 2 receptors. Sackheim et al. (24) have found diminished frontal, superior temporal, and anterior parietal blood flow, while Baxter et al. (21) reported diminished left frontal blood flow in depression. These blood flow, neuropathological, and neurochemical studies and the present MRI study demonstrate that elderly depressed patients have both functional and structural cortical abnormalities.

The prognostic significance of these changes is unclear. Although they are in the same direction as the changes seen in patients with Alzheimer's disease, it is unlikely that they reflect early Alzheimer's disease in most cases, since the prognosis of depression in old age is different from the prognosis of dementia (25).

Larger samples might well show differences between depression and Alzheimer's disease, since the group with Alzheimer's disease had greater changes on seven of the MRI measures. However, it is of note that depressed patients were nonsignificantly worse than Alzheimer's disease subjects on basal ganglia lesion severity and sylvian fissure severity. Basal ganglia changes have been linked to depression (26, 27), and we have previously demonstrated language changes in depressed patients with cognitive impairment (28). The latter suggests temporal lobe changes that are perhaps reflected in sylvian fissure atrophy.

The conclusion that the MRI lesions in Alzheimer's disease and depression differ in prognostic significance is supported by a recent long-term follow-up of three elderly depressed patients with extensive white matter hyperintensities (29) that found no development of dementia and by a study of normal elderly subjects (30) that found no correlation between extent of white matter hyperintensities and cognitive performance after controlling for age. Further study should clarify whether the cortical MRI changes in depression are related to clinical severity, treatment resistance, mortality, or the development of a progressive dementia. A study of never-treated depressed subjects would clarify whether pharmacotherapy might have induced these changes and would test the hypothesis that these lesions coincide with and possibly predate the development of affective disorder.

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# Changes in Brain Glucose Metabolism in Cocaine Dependence and Withdrawal

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*Objective: The authors investigated changes in brain function associated with cocaine dependence and withdrawal to provide clues regarding the processes that lead to the uncontrollable self-administration of cocaine. Method: They measured regional brain metabolism with [$^{18}$F]-fluorodeoxyglucose (FDG) and positron emission tomography in 15 outpatients with the diagnosis of cocaine abuse and 17 normal comparison subjects. Ten of the patients were studied less than 1 week after they had last had cocaine, and five were studied 2–4 weeks after withdrawal. Results: Patients studied within 1 week of cocaine withdrawal but not those studied within 2–4 weeks of cocaine withdrawal had higher levels of global brain metabolism as well as higher levels of regional brain metabolism in the basal ganglia and orbitofrontal cortex than did normal subjects, probably as a consequence of less brain dopamine activity. There was also a significant relationship between the number of days since cocaine withdrawal and regional brain glucose metabolism in the orbitofrontal cortex and in the basal ganglia, and the correlations between cocaine craving and metabolic activity were significant in the prefrontal cortex and the orbitofrontal cortex. Conclusions: Although the time-dependent fall in metabolic activity suggests that the higher metabolic activity observed less than a week after cocaine withdrawal may represent a nonspecific expression of drug withdrawal, the selectivity of changes in glucose metabolism for the basal ganglia and for the orbitofrontal cortex suggests that the regional metabolic changes seen in cocaine abusers during detoxification are related to changes in brain dopamine activity.*

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Cocaine has been characterized as one of the most reinforcing drugs of abuse (1). Under conditions of free availability, cocaine will induce insatiable repeated self-administration (2) terminated only by physical exhaustion or by extinction of the drug supply (3). The reinforcing properties of cocaine have been related to its euphorigenic actions, which in turn have been linked to cocaine's ability to block dopamine reuptake (4–7). We hypothesized that although the euphorigenic actions of cocaine initiate self-administration, this is not the sole mechanism leading to its compulsive use, since compulsive cocaine use occurs even in the face of tolerance to the euphorigenic actions of cocaine (8, 9). Investigation of regional brain changes associated with cocaine dependence may provide clues about the processes that lead to the uncontrollable self-administration of cocaine.

Positron emission tomography (PET) and [$^{18}$F]-fluorodeoxyglucose (FDG) have been useful in identifying areas of brain dysfunction that characterize patients with different psychiatric and neurological diseases (10). Previous studies of cocaine with PET have investigated the actions of chronic cocaine on cerebral blood flow (11), dopamine receptors (12), and brain dopamine metabolism (13) and the actions of acute cocaine on brain metabolism (14). PET has also been used to monitor cocaine binding and kinetics in the human brain (7). In the present study, we investigated the patterns of regional brain metabolism in chronic cocaine abusers at different times after cocaine withdrawal to determine whether we could observe

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**TABLE 1. Demographic and Clinical Characteristics of 15 Cocaine Abusers**

| | | Cocaine Use | | | | |
|---|---|---|---|---|---|---|
| Subject | Age (years) | Time Since Last Use (days) | Duration (years) | Amount (g/week) | Affective Symptoms[a] | Cocaine Craving[b] |
| 1 | 24 | 1 | 6 | 10 | Mild | Severe |
| 2 | 26 | 1 | 1 | 7 | Mild | Moderate |
| 3 | 26 | 1 | 2 | 18 | Severe | Severe |
| 4 | 37 | 1 | 3 | 4 | None | Moderate |
| 5 | 31 | 3 | 4 | 20 | Mild | Severe |
| 6 | 28 | 4 | 8 | 14 | Mild | Moderate |
| 7 | 29 | 5 | 10 | 10 | Moderate | Severe |
| 8 | 18 | 6 | 4 | 16 | Moderate | Severe |
| 9 | 30 | 7 | 7 | 15 | Severe | Severe |
| 10 | 27 | 7 | 6 | 7 | None | Moderate |
| 11 | 29 | 15 | 2 | 28 | Severe | Moderate |
| 12 | 30 | 17 | 2 | 5 | Moderate | Mild |
| 13 | 38 | 21 | 6 | 5 | Severe | Moderate |
| 14 | 28 | 29 | 7 | 20 | None | Mild |
| 15 | 30 | 30 | 6 | 7 | Mild | Mild |

[a] Affective symptoms were rated with the Beck Depression Inventory.

[b] Cocaine craving was rated for the week that preceded the PET scan by asking patients to rate the frequency and the intensity of cocaine craving.

changes in regional brain function that might disclose the patterns of brain dysfunction associated with cocaine dependence and withdrawal.

## METHOD

This study was carried out following the guidelines established by the Human Studies Review Committee at our laboratory. All subjects provided written informed consent.

The 15 outpatients included in the study met *DSM-III-R* criteria for a diagnosis of cocaine dependence. These patients were men with a mean±SD age of 29±5 years who had abused cocaine for at least 12 months, mainly in the form of free base (crack). The patients had taken at least 4 g/week of cocaine for 6 months before the beginning of the study and had been drug-free for no more than 1 week during the 6 months that preceded the study. Ten patients were studied between 12 hours and 1 week after their last use of cocaine and five patients were studied between 2 and 4 weeks after their last use of the drug. Although all of the patients had a positive history for alcohol, nicotine, marijuana, and/or minor tranquilizer use, none of them was addicted to any of these drugs except nicotine.

Affective symptoms were recorded by using the Beck Depression Inventory, which was given 1 day before the PET scan. Craving for cocaine was rated for the week that preceded the PET scan by asking patients to rate the frequency and intensity of their cocaine craving as none, mild, moderate, or severe. Table 1 provides demographic and clinical information about the patients.

The group of normal comparison subjects consisted of 17 right-handed male volunteers 32±4 years old who had no neurological or psychiatric disease according to examination and who had no history of drug or alcohol abuse in themselves or in their first-degree relatives. None of the comparison subjects had a current or past history of drug and/or alcohol abuse except for nicotine.

All of the patients and comparison subjects were without abnormalities according to general physical examination. Except for cocaine, none of the patients or comparison subjects had been receiving any medication for at least 1 month before the study.

All subjects were scanned with a PET VI instrument in the high resolution mode (full-width half-maximum 0.9 cm). In preparation for the study, two venous catheters were installed for FDG injection and for arterialized plasma sampling. Positioning of the subject in the PET scanner was accomplished by using an individual headholder and two sets of orthogonal lasers positioned parallel to the canthomeatal line and parallel to the sagittal plane. The subjects' heads were fixed into the headholder with a chin strap. Before the radionuclide emission scans, the subjects underwent a set of two transmission scans positioned 7.2 mm apart from the canthomeatal line. Transmission scans were performed with a ring filled with gallium-68 to correct for attenuation. The subjects were injected with 6–8 mCi of FDG while they were kept in a quiet and dimly lit room in the supine position. They were asked to keep their eyes open, and their ears were not plugged.

Scanning was started 35 minutes after the FDG injection, and two sequential brain scans of 8 minutes each taken 7.2 mm apart were obtained at 35 and 44 minutes after the injection. Arterialized blood sampling and determinations of plasma glucose and F-18 concentration have been described elsewhere (15).

The FDG images were transformed into metabolic images by using the operational model of Sokoloff et al. (16) extended by Phelps et al. (17) and Huang et al. (18). The rate constants and lumped constants used were those reported by Reivich et al. (19). Fourteen parallel brain slices positioned 7.2 mm apart were obtained. Nine cortical, two subcortical, and one cerebellar region were selected from these slices. Values for each region were obtained by averaging the weighted values of a given region across slices. A global brain metabolic value was obtained by averaging the metabolic rate for the five central slices. The 12 regions of interest were drawn directly onto the PET scan by using a template for the different brain slices as a reference (figure 1). The position of the regions was adjusted manually to each individual slice. The regions on the slice template were obtained by using Matsui and Hirano's atlas (20).

Differences in regional glucose metabolism among normal subjects, chronic cocaine abusers who had last had cocaine less than a week before scanning, and cocaine abusers who had last had the drug 2–4 weeks before scanning were analyzed by using one-way analysis of variance (ANOVA). Post hoc t tests with Bonferroni's correction for multiple tests were used to test differences between groups ($p \le 0.004$). For those brain regions where the glucose metabolism of normal subjects was found to be significantly different from that of cocaine abusers, the effects of cocaine withdrawal on regional brain glucose metabolism were tested by using regression analyses between the number of days since the patient's last use of cocaine and the regional brain glucose metabolism.

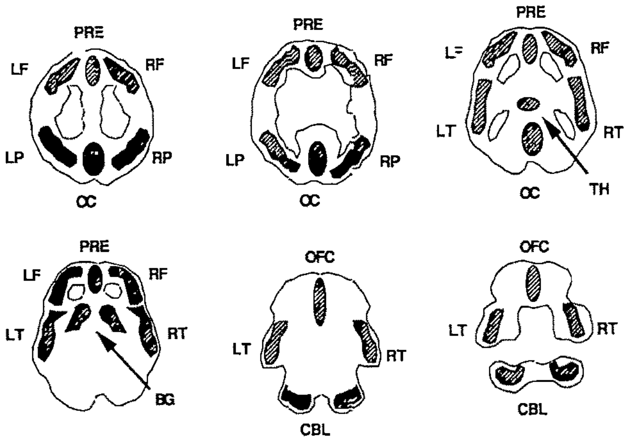
The relationships between glucose metabolism and cocaine craving and affective symptoms for the 12 brain regions were tested by using Pearson product-moment correlation coefficients. Because of the multiple comparisons, only correlations with $p \le 0.01$ were considered significant.

## RESULTS

All but three of the cocaine-dependent patients had depressive symptoms at the time of the study (table 1). All 15 patients had some evidence of cocaine craving, even after 30 days of detoxification. There was a tendency for those patients who were tested after 15 days of detoxification to have less craving than the patients tested during early detoxification.

Global brain glucose metabolism was significantly higher in cocaine abusers tested during early withdrawal (less than 1 week after they had last had cocaine) than in normal subjects or in cocaine abusers tested during late withdrawal (1–4 weeks after they had last had cocaine). Table 2 gives the metabolic values for the different brain regions of the normal subjects and the two groups of cocaine abusers. Significant differences among the three groups were seen in global glucose metabolism, in the orbitofrontal cortex, and in the basal ganglia (table 2). The post hoc t tests performed to assess differences between normal subjects and cocaine abusers who had last had the drug less than a week before scanning and between normal subjects and cocaine abusers who had not had the drug for 2–4 weeks revealed no differences between the normal subjects and the cocaine abusers who had not had the drug for 2–4 weeks. In contrast, there was a significant difference between the normal subjects and the patients who had been withdrawn from cocaine for less than a week in glucose metabolism in the orbitofrontal cortex (unpaired t value=−3.90, df=23, $p \le 0.0007$).

FIGURE 1. Template Used to Define Regions of Interest on Metabolic Images[a]



[a] PRE=prefrontal, LF=left frontal, RF=right frontal, LP=left parietal, RP=right parietal, OC=occipital, LT=left temporal, RT=right temporal, TH=thalamus, BG=basal ganglia, OFC=orbitofrontal cortex, CBL=cerebellum.

Regression analyses revealed a significant relationship between the number of days since cocaine withdrawal and regional brain glucose metabolism for the orbitofrontal cortex ($y=0.062x+7.576$, $r^2=0.52$, $p \le 0.003$) and for the basal ganglia ($y=0.026x+8.189$, $r^2=0.39$, $p \le 0.02$). Figure 2 shows the regression analysis for the orbitofrontal cortex; the brain glucose metabolism decreased as the amount of time since withdrawal from cocaine increased.

We found no significant relationships between regional glucose metabolism and affective symptoms as scored by the Beck Depression Inventory. The correlations between cocaine craving and metabolic activity were significant for the prefrontal cortex ($r=0.70$, df=14, $p=0.004$) and for the orbitofrontal cortex ($r=0.63$, df=14, $p=0.01$).

## DISCUSSION

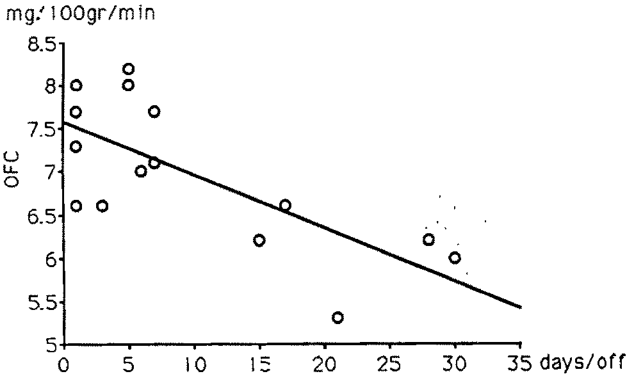
We found that the regional brain glucose metabolism of recently withdrawn cocaine abusers was higher than that of normal control subjects, particularly in the orbitofrontal cortex and basal ganglia. We found no significant differences in regional brain glucose metabolism between normal control subjects and cocaine

**TABLE 2. Regional Brain Glucose Metabolism of 17 Normal Comparison Subjects and 15 Cocaine Abusers**

| | Metabolism (mg/100 g per minute) | | | | | |
|---|---|---|---|---|---|---|
| | Normal Subjects (N=17) | | Cocaine Withdrawn for Less Than 1 Week (N=10) | | Cocaine Withdrawn for 2–4 Weeks (N=5) | |
| Brain Region | Mean | SD | Mean | SD | Mean | SD |
| Global[a] | 5.4 | 0.6 | 6.0 | 0.5 | 5.4 | 0.5 |
| Prefrontal | 6.6 | 0.9 | 7.1 | 0.6 | 6.1 | 0.6 |
| Orbitofrontal[b] | 6.3 | 0.9 | 7.5 | 0.5 | 6.1 | 0.5 |
| Left frontal | 5.9 | 0.9 | 6.5 | 0.7 | 5.5 | 0.3 |
| Right frontal | 6.1 | 0.8 | 6.7 | 0.7 | 5.8 | 0.3 |
| Left parietal | 6.0 | 0.8 | 6.6 | 0.8 | 5.8 | 0.6 |
| Right parietal | 6.0 | 0.8 | 6.6 | 0.9 | 5.9 | 0.7 |
| Left temporal | 6.2 | 0.8 | 6.7 | 0.4 | 6.0 | 0.4 |
| Right temporal | 6.3 | 0.8 | 6.8 | 0.6 | 6.4 | 0.4 |
| Occipital | 8.1 | 1.1 | 8.7 | 0.8 | 8.4 | 1.3 |
| Thalamus | 7.4 | 1.0 | 7.9 | 0.8 | 7.9 | 1.3 |
| Basal ganglia[c] | 7.3 | 0.9 | 8.1 | 0.4 | 7.4 | 0.5 |
| Cerebellum | 5.7 | 0.7 | 6.0 | 0.8 | 5.2 | 0.9 |

[a] Significant differences among the groups: F=3.94, df=2, 29, $p\leq0.05$.
[b] Significant differences among the groups: F=7.55, df=2, 29, $p\leq0.01$.
[c] Significant differences among the groups: F=3.33, df=2, 29, $p\leq0.05$.

**FIGURE 2. Regression Analysis for Regional Brain Glucose Metabolism in Orbitofrontal Cortex (OFC) and Number of Days Off Cocaine[a]**



[a] $r^2=0.52$, df=14, $p\leq0.003$.

abusers tested 2–4 weeks after cocaine withdrawal. The time-dependent fall in metabolic activity suggests that the higher metabolic activity observed less than a week after cocaine withdrawal may represent a nonspecific expression of drug withdrawal. Withdrawal from stimulants has been shown to produce an excitatory state secondary to release of epinephrine and norepinephrine from the sympathetic nervous system (21). However, the selectivity of changes in glucose metabolism for the basal ganglia, which has the highest density of dopamine receptors, and for the orbitofrontal cortex, which is one of the main projections of the mesocortical dopamine system (22), suggests that the regional metabolic changes seen in the cocaine abusers during detoxification may be related to changes in brain dopamine activity. In fact, using PET and dopamine$_2$ specific tracers, we have documented that there is decreased dopamine receptor availability in the basal ganglia of recently detoxified cocaine abusers (12).

Although the role of dopamine in the control of glucose metabolism in the human brain is poorly understood, there are some data suggesting that acute administration of drugs which increase dopamine activity, such as cocaine (14) and amphetamine (23), decrease brain glucose metabolism. There are also some data suggesting that inhibition of brain dopamine activity with chronic neuroleptic treatment leads to an increase in regional brain metabolism (24, 25). Hypermetabolic activity in the recently detoxified cocaine abuser would be consistent with a decrease in brain dopamine activity, an effect that is predominantly seen in areas rich in dopamine receptors and areas innervated by the dopamine system. However, the disruption of other neurotransmitter systems in response to chronic use of cocaine could also affect regional brain metabolism.

Greater metabolic activity of the orbitofrontal cortex and basal ganglia has been reported in patients with obsessive-compulsive disorders (26, 27). This may be of relevance to the present study because the orbitofrontal cortex and the basal ganglia form part of a circuit that has been postulated to play a critical role in the occurrence of repetitive behaviors in patients with obsessive-compulsive disorder (28). Animal experiments have shown that lesions of this circuit lead to the emergence of repetitive behaviors that cannot be terminated by external or internal cues (29). Whether inhibition of this circuit by cocaine could trigger the compulsive pattern of cocaine self-administration is an interesting unresolved question. In this study we found a significant positive correlation between cocaine craving and metabolic activity in the orbitofrontal cortex and the prefrontal cortex. However, the relationship between the orbitofrontal cortex and cocaine craving needs to be interpreted cautiously because metabolic activity in the orbitofrontal cortex was strongly correlated with the amount of time since last cocaine use and cocaine craving has been shown to decrease as the period of withdrawal increases (3). In addition, although cocaine craving is a good predictor of relapse, it is not a measure of compulsive cocaine use. Demonstration of involvement of the orbitofrontal cortex in the compulsive pattern of cocaine self-administration would require investigation of the cocaine abuser during compulsive cocaine self-administration.

The association of cocaine abuse and compulsive behavior is not a new one. Purposeless repetitive behavior in cocaine abusers was described at the beginning of the century (30). Cocaine has also been shown to exacerbate compulsive behavior in patients with obsessive-compulsive disorder (31, 32). Furthermore, amphetamine-induced stereotypic behavior has been proposed as a model for compulsive behavior (33).

Within this context, however, it should be noted that the conceptualization of compulsive cocaine use as somehow involving similar brain circuits to the ones implicated in obsessive-compulsive disorder does not imply that these are variants of the same disorder. Disruption of a particular brain functional system can occur through different mechanisms and may represent just a part of a more complex pattern of brain dysfunction.

In analyzing the effects of chronic use of cocaine on regional brain glucose metabolism, one should also take into account the effects of chronic cocaine abuse on cerebral blood flow (CBF) because chronic cocaine use can lead to lower CBF and cerebrovascular accidents (11). Disturbances in CBF could in turn generate disturbances in brain metabolism. Comparison of regional defects in CBF and in glucose metabolism could help to further clarify this relationship.

Several cautionary statements should be made about this study. First, a crossover design was used; a longitudinal study would provide a better grasp of the evolution of the changes in brain glucose metabolism during the different phases of cocaine withdrawal. Second, all of the patients in this study, although dependent only on cocaine, abused other drugs as well, and interactions among drugs could affect the patterns of regional brain glucose metabolism. Third, the pattern of metabolic dysfunction after prolonged detoxification cannot yet be assessed from this study because we examined only five subjects who had not had cocaine for 2–4 weeks. Larger samples as well as longer periods of cocaine withdrawal need to be studied to determine long-term consequences of cocaine use on regional brain glucose metabolism. Finally, the possibility that preexisting patterns of regional brain function may predispose individuals to the use of cocaine needs to be further evaluated.

In summary, this study shows that cocaine abusers who were in the early phase of withdrawal had higher levels of metabolic activity in the orbitofrontal cortex and basal ganglia, probably as a consequence of lower brain dopamine activity.

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# Comparison of Acetorphan With Clonidine for Opiate Withdrawal Symptoms

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Objective and Method: *The authors compared the effects of acetorphan, an enkephalinase inhibitor, with those of clonidine for the treatment of the opioid withdrawal syndrome. Nineteen patients addicted to heroin or synthetic opiates who were undergoing drug withdrawal and displayed a withdrawal syndrome according to* DSM-III *criteria were studied for 5 days in a hospital setting. In a double-blind trial, 10 subjects were given acetorphan intravenously and nine were given clonidine; objective signs and subjective symptoms of withdrawal were recorded.* Results: *On several objective signs, the effect of acetorphan was more marked than that of clonidine, whereas the two drugs exhibited similar efficacy with respect to the subjective components of withdrawal. No side effect was noted in the subjects who received acetorphan.* Conclusions: *Enkephalinase inhibition may constitute a novel and safe therapeutic approach to the opioid withdrawal syndrome.*

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Although the neurochemical mechanisms responsible for addiction to opioids are still debated, the withdrawal syndrome is thought to involve a functional deficiency in endogenous opioid peptides (1). Thus, chronic administration of morphine may decrease enkephalinergic transmissions in the brain (2), and the withdrawal syndrome is ameliorated by opioid peptides and exacerbated by opiate antagonists (1). Protection of endogenous enkephalins, through inhibition of the peptidases responsible for their inactivation, might therefore constitute a novel approach to treatment of the opioid withdrawal syndrome. In animals, inhibitors of enkephalinase (EC 3.4.24.11, neutral metalloendopeptidase) protect endogenous enkephalins from degradation and thereby elicit a number of opioid-like effects that are reversible with naloxone (3). Furthermore, several enkephalinase inhibitors attenuate the severity of naloxone-precipitated opiate withdrawal symptoms in rodents (4, 5).

The recent availability of acetorphan—a parenterally active enkephalinase inhibitor that does not produce drug dependence (6, 7) and the safety of which has now been established in several hundred patients—made it feasible to test the enkephalinase inhibitor hypothesis in human beings for the first time. Using a double-blind trial, we compared the effects of acetorphan in opiate withdrawal to those of clonidine, the efficacy of which is well-established in detoxification but which has some side effects, such as severe hypotension (8).

## METHOD

The study included 13 male subjects and six female subjects without concurrent psychiatric diagnoses who had been addicted to heroin (N=16) or synthetic opiates (N=3) from a mean±SD age of 18±3 years. Their most recent drug addiction period had lasted for a mean±SD 8.3±6.4 months, and the last drug intake had occurred 8.5±7.2 hours before admission to the hospital. Patients with kidney or heart disease, epilepsy, allergy, or a high intake of benzodiazepines or barbiturates were excluded. Patients included in the study displayed on day 1 (i.e., 24 hours after admission) an opioid withdrawal syndrome according to the *DSM-III* criteria. They were randomly distributed into two groups and treated in a double-blind fashion for 3 days, starting at 9:00 a.m. on day 1. Since acetorphan

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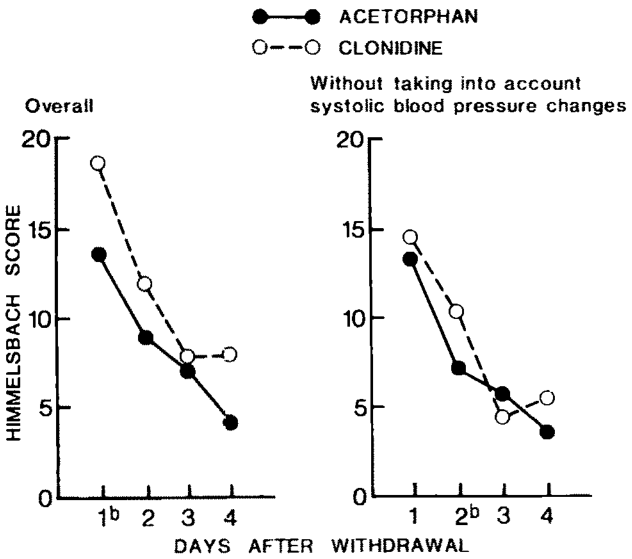
**FIGURE 1. Effects of Acetorphan and Clonidine on Objective Signs of Withdrawal From Opiates Rated on the Himmelsbach Scale[a]**



[a] Treatments were started on day 1.
[b] $p<0.05$, Mann-Whitney test.

must be administered intravenously to cross the blood-brain barrier (9), the following design was adopted. The first group (seven male and three female subjects aged 27±3 years and weighing 62±8 kg) received acetorphan, 50 mg i.v. (a dose selected from pharmacokinetic studies), at 9:00 a.m. and 5:00 p.m. and placebo capsules at 9:00 a.m. and 1:00, 5:00, 9:00, and 11:00 p.m. The second group (six male and three female subjects aged 26±5 years and weighing 58±6 kg) received 0.075 mg of clonidine in capsule form at 9:00 a.m. and 1:00, 5:00, 9:00, and 11:00 p.m. and placebo infusions at 9:00 a.m. and 5:00 p.m.

The patients were observed for objective signs of withdrawal (i.e., anorexia, diarrhea, mydriasis, tremors, "goose flesh," perspiration, emesis, yawning, lacrimation, rhinorrhea, and restlessness) and for physiological parameters (blood pressure, respiratory rate, and body temperature). All of these signs were recorded, and a score for objective signs on the Himmelsbach scale (10) was calculated every hour from 9:00 a.m. to 1:00 p.m. each day. Weight was measured every day at 9:00 a.m. Subjective reports of withdrawal symptoms were evaluated every day at 9:00 a.m. and 1:00 p.m. on the Opiate Withdrawal Scale from the Addiction Research Center Inventory (11), which includes 29 items (e.g., "I feel sluggish," "My mouth is very dry"). The subjects' interruption of opiate intake was checked by urinalysis throughout the study.

Data were analyzed by analysis of variance analysis (ANOVA) for repeated measures with BMDP software. The main sources of variance we considered were subjects, drugs, time, and their interaction. Pairwise comparisons were done with Mann-Whitney and Wilcoxon nonparametric two-tailed tests or, when authorized by the distributions, Student's two-tailed t test.

## RESULTS

The two groups were found to be comparable (Mann-Whitney nonparametric test) in age, sex, nature of opiates used, age at first opiate intake, usual daily intake, duration of last addiction period, and last drug intake prior to admission. On day 1 at 9:00 a.m. (i.e., before treatment), although the two groups displayed rather high initial scores for objective signs of withdrawal, the mean score was significantly higher in the clonidine group than in the acetorphan group ($p=0.05$, Mann-Whitney test), a difference attributable to a higher mean blood pressure in the clonidine group before initiation of treatment (figure 1).

With both treatments the overall daily score for objective signs (figure 1, left side) was significantly lower starting on day 2 ($p<0.05$ and $p<0.02$ for acetorphan and clonidine, respectively; Wilcoxon test); the change was more marked ($p=0.02$) with acetorphan on day 2 if blood pressure was not taken into account in the total score (figure 1, right side).

When individual objective signs were considered, no major differences between the two groups appeared from the ANOVA with one between-group factor (drug) and one within-group factor (day). Diarrhea was slightly more improved by acetorphan ($p=0.10$). Lacrimation was significantly more improved in the acetorphan group ($p=0.02$), and the same was true for weight loss, but this sign was (nonsignificantly) higher at the start of treatment in this group. Tachypnea, hypertension, and hyperthermia did not differ between the two groups during treatment (data not shown). Hourly assessment of objective symptoms during day 1 indicated that the changes in overall scores did not significantly differ in the two groups (data not shown).

Subjective withdrawal symptoms (scores on the Opiate Withdrawal Scale), which were similar in the two groups before initiation of treatment, fell gradually and reached a significant difference from baseline on day 4 ($p=0.008$ for clonidine and $p=0.02$ for acetorphan; two-tailed Wilcoxon test). There was no significant difference between the two groups in the ANOVA with one between-group factor (drug) and one within-group factor (time) when data were analyzed daily or hourly during day 1 (data not shown).

No side effect was recorded with acetorphan, whereas one patient treated with clonidine displayed feelings of faintness associated with severe hypotension on day 1. Patients complaining of insomnia were given an alimemazine tablet, 50 mg, in the evening; the mean±SD numbers of these tablets given during the trial (2.5±0.4 and 2.0±0.5 in the acetorphan and clonidine groups, respectively) did not differ between the two groups.

## DISCUSSION

The results of this study suggest that acetorphan is at least as effective as clonidine in preventing objective signs and subjective symptoms of opiate withdrawal. There was a more rapid effect of acetorphan on objective symptoms scored on the Himmelsbach scale, except for systolic blood pressure (because the two groups were found to differ on this symptom before starting treatment). This superior action of acetorphan was based on a significantly more rapid suppression of some individual symptoms, i.e., lacrimation and weight loss, and similar trends for anorexia and diarrhea, although the differences for these last two symptoms failed to reach significance. Weight loss during withdrawal is mainly a consequence of diarrhea, and acetorphan displays antidiarrheal activity that is reversible with naloxone (6, 12).

The effects of acetorphan, like those of clonidine (8), seemed less rapid for subjective symptoms than for objective signs, and the decrease in Opiate Withdrawal Scale scores reached significance only on day 4. However, it should be remembered that in the absence of any treatment, both subjective symptoms and objective signs steadily increase to a peak at 2–3 days after withdrawal (1). No side effect was recorded in the acetorphan group, whereas one subject receiving clonidine experienced severe hypotension, a well-known effect of this drug. The efficacy of acetorphan in this study is consistent with the (partial) suppressive effects of enkephalinase inhibitors found in rodent models of naloxone-precipitated withdrawal (4, 5), in which, however, their naloxone-reversible effects (3) are likely to be blunted.

Increased noradrenergic transmission in the CNS plays a pivotal role in the opioid withdrawal syndrome (1, 9, 13). The efficacy of clonidine and acetorphan for withdrawal symptoms may be largely derived from the decrease in noradrenaline release they elicit through stimulation of presynaptic $\alpha_2$-adrenergic (9) and opiate (13) receptors, respectively, the latter being mediated by endogenous enkephalins protected from degradation (6). The naloxone-reversible increase in cerebral serotonin turnover elicited by acetorphan (6) might also contribute. Finally, since enkephalinase inhibitors still suppress some withdrawal symptoms in naloxone-treated rodents (4, 5), protection of nonopioid peptides known to be substrates of enkephalinase (2) may also be involved.

The positive results of the present trial suggest that enkephalinase inhibition may constitute a novel and safe therapeutic approach to the management of the opioid withdrawal syndrome.

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# Outcomes for Cocaine Abusers After Once-a-Week Psychosocial Therapy

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*Objective: The authors studied the efficacy of once-weekly psychotherapy, family therapy, or group therapy led by paraprofessionals among patients with cocaine use disorders. Method: Of subjects who sought outpatient treatment, 168 consented to participate in the study and were each randomly assigned to one of the three forms of therapy; 122 patients were interviewed 6–12 months later. Their pre- and posttreatment scores on the Addiction Severity Index were compared. Results: Significant improvements were observed for the cohort as a whole, but virtually all of the improvement was restricted to the 23 subjects (19%) who were not using cocaine at follow-up. There was a strong relationship between abstinence from cocaine use and absence of addiction-related problems, especially psychiatric symptoms and family problems. Conclusions: The results of the study indicate that outpatient therapy once a week is ineffective for cocaine use disorder. The 19% abstinence rate probably represents spontaneous remission among patients with enough motivation to seek treatment, as the number of therapy sessions attended was not related to improvement. Either an intense level of outpatient contact or residential treatment followed by aftercare is probably needed, at least initially, while the patient is attempting to initiate and sustain abstinence.*

(Am J Psychiatry 1991; 148:630–635)

Of illicit drugs, cocaine is the object of the most profound concern, and it is the only illicit substance whose use increased through the mid-1980s (1). A number of studies have reported social and psychological characteristics of cocaine users (2–6), and a variety of different treatments have been attempted (7–11). However, there have been few follow-up studies of any form of treatment (12 and unpublished study of D. Waldorf et al., 1988), and information about use patterns over extended periods is sparse. As with other addictive drugs, there is uncertainty about the extent to which recovery is possible and about the ways in which treatment affects the recovery process (13). This paper focuses on important aspects of the lives of a group of crack and cocaine addicts who applied for once-weekly therapy as part of a treatment outcome study. They were interviewed at two times—at the first treatment contact and at follow-up 6–12 months later. The study was designed to compare the efficacy of family therapy, psychotherapy, and group therapy led by paraprofessionals as treatments for cocaine abuse.

We compared the initial and follow-up levels of cocaine or crack use for the group and examined the effect of number of therapy sessions on level of cocaine use at follow-up. We also compared other drug use and other problems in the subjects who stopped using cocaine and those who did not, at both intake and follow-up.

## METHOD

### Subjects

The analysis is based on follow-up data collected from 122 adults with cocaine use disorder who participated in a study of outpatient treatment for drug abuse. The patients who consented to participate in the study were each randomly assigned to receive once-weekly family therapy, individual supportive-expressive psychotherapy, or group therapy led by paraprofessionals. They were assessed at initial contact and 6 to 12 months later. Our intention was to conduct follow-up interviews 6 months after the initial contact, but difficulties in locating certain subjects produced a

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**TABLE 1. Demographic Characteristics of Cocaine Abusers Assessed Before and After Once-a-Week Psychosocial Treatment**

| Variable | Baseline (N=168) N | Baseline (N=168) % | Follow-Up (N=122) N | Follow-Up (N=122) % |
|---|---|---|---|---|
| Sex | | | | |
| Male | 145 | 86 | 104 | 85 |
| Female | 23 | 14 | 18 | 15 |
| Education | | | | |
| <12 years | 44 | 26 | 30 | 25 |
| 12 years | 69 | 41 | 49 | 40 |
| >12 years | 55 | 33 | 43 | 35 |
| Age (years) | | | | |
| 20–29 | 87 | 52 | 56 | 46 |
| 30–39 | 67 | 40 | 56 | 46 |
| 40–49 | 14 | 8 | 10 | 8 |
| Ethnicity | | | | |
| Non-Hispanic white | 27 | 16 | 20 | 16 |
| Black | 104 | 62 | 79 | 65 |
| Hispanic | 35 | 21 | 23 | 19 |
| Other | 2 | 1 | 0 | 0 |
| Occupation | | | | |
| White-collar | 54 | 32 | 41 | 34 |
| Blue-collar or unemployed | 114 | 68 | 81 | 66 |

time lag that was longer than expected for those who were hardest to reach. The 122 persons evaluated at follow-up represent 73% of the 168 who were seen originally.

All persons admitted to the study were classified at intake in terms of both lifetime and current cocaine use disorders according to *DSM-III-R* criteria. At the time of entry, their history of cocaine use ranged from 1 to 31 years; the mean was 8 years. The reinterviewed patients closely resembled the baseline group in terms of demographic characteristics (see table 1). The majority of subjects in each group were nonwhite men with 12 or fewer years of education. Most had held full-time jobs in the 3 years before entry into treatment, and of these, the majority had blue-collar jobs. More than one-half had been arrested at least once, about two-thirds of these on non-drug-related charges. The demographic characteristics of the baseline group of 168 subjects are presented in table 1 for comparison of the baseline and follow-up groups, but the analysis in this study is based solely on the 122 subjects who were interviewed at both intake and follow-up.

### *Measures*

Each subject received an extensive battery of tests at intake. The evaluation was conducted over two scheduled appointments and required approximately 5 hours to complete. The measures selected for analysis in this paper were a subset of those completed—the Addiction Severity Index (14) and a drug history instrument designed by us.

The Addiction Severity Index is a structured clinical research interview designed to provide information about areas of a patient's life in which there is often dysfunction associated with drug abuse. These potential problem areas are 1) medical, 2) legal, 3) drug, 4) alcohol, 5) employment, 6) family/social, and 7) psychiatric. Reliability and validity data for the Addiction Severity Index have been extensively reported (14–17), and it has become one of the most commonly used evaluation instruments in clinical studies of substance use disorders. A composite score, based on the sum of the scores for several individual questions within each problem area, has been developed for each area by P.L. McGahan et al. (unpublished work) and is used in this paper.

The drug history instrument is a structured interview designed for this study to describe past and current cocaine use in detail. It also includes questions about age at first cigarette use, level of current cigarette smoking, first illicit drug used, age at which that drug was used, and other drugs used both at the beginning of cocaine use and during the period of heaviest cocaine use. In addition, a measure of abstinence from cocaine use at follow-up was developed by combining the results of urine testing with self-report at follow-up.

### *Analysis*

Paired t tests were used to determine the significance of the difference in means between baseline and follow-up for the same group. We performed analysis of covariance to test differences between the mean scores of the two groups at follow-up, using the group means at baseline as covariates, and determined significance with the F test.

## RESULTS

For the 122 subjects interviewed at both baseline and follow-up, the mean age at first cocaine use was 22 years, and the range was 12 to 45 years. The mean age at first use of any illicit drug was 17 years; the range was 11 to 39. Almost all (91%) of the subjects (N=111) had used cocaine several times a week or more for at least 1 month, and 34% (N=41) had used the drug that often for 4 years or more. Although 96% (N=117) had begun by using cocaine intranasally ("snorting"), crack or free-base inhalation was the current ingestion route for 72% of the group (N=88) in the 30 days before the first program contact. About one-half (46%, N=56) spent over $400 on cocaine and/or crack in the 30 days before entering treatment.

As expected, about three-fourths of the patients (73%, N=89) were users of cigarettes, alcohol, and marijuana, as well as cocaine. One-quarter (26%, N=32) had drunk alcohol to intoxication at least three times a week for 1 month or more at some time in their lives. Seventy-one percent (N=87) had used marijuana at least three times a week for at least 5 months. Regular use of other drugs was lower: 14% (N=17) had

**TABLE 2. Addiction Severity Index Scores of 122 Cocaine Abusers Before and After Once-a-Week Psychosocial Treatment**

| Addiction Severity Index Measure[a] | Baseline | | Follow-Up | | Two-Tailed t Test | | |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | t | df | p |
| Drug composite | 0.2 | 0.1 | 0.1 | 0.1 | 9.32 | 110 | <0.001 |
| Days of cocaine use | 11.5 | 9.1 | 5.5 | 8.5 | 5.85 | 114 | <0.001 |
| Days of marijuana use | 4.8 | 8.1 | 2.1 | 4.8 | 3.82 | 114 | <0.001 |
| Dollars[b] spent on drugs | 8.4 | 6.8 | 2.9 | 4.5 | 7.98 | 113 | <0.001 |
| Days of drug problems | 14.4 | 12.4 | 7.2 | 11.0 | 5.20 | 114 | <0.001 |
| Alcohol composite | 0.1 | 0.1 | 0.1 | 0.1 | 1.02 | 113 | n.s. |
| Days of alcohol use | 1.1 | 3.5 | 1.9 | 3.6 | −1.97 | 114 | 0.05 |
| Dollars[b] spent on alcohol | 1.2 | 2.1 | 0.8 | 1.0 | 1.89 | 114 | n.s. |
| Days of alcohol problems | 0.5 | 3.3 | 0.6 | 3.5 | −0.31 | 114 | n.s. |
| Medical composite | 0.2 | 0.3 | 0.1 | 0.2 | 1.16 | 111 | n.s. |
| Days of medical problems | 2.7 | 6.8 | 2.1 | 5.1 | 0.95 | 112 | n.s. |
| Employment composite | 0.6 | 0.3 | 0.6 | 0.3 | −0.14 | 105 | n.s. |
| Days worked[c] | 13.9 | 11.8 | 13.0 | 10.7 | 0.72 | 114 | n.s. |
| Dollars[b] earned[c] | 11.6 | 9.3 | 10.5 | 8.9 | 1.11 | 112 | n.s. |
| Legal composite | 0.1 | 0.1 | 0.1 | 0.1 | 1.11 | 102 | n.s. |
| Days of criminal activity | 0.6 | 3.2 | 0.2 | 1.0 | 1.47 | 109 | n.s. |
| Family/social composite | 0.4 | 0.2 | 0.3 | 0.2 | 6.44 | 104 | <0.001 |
| Days of problems with family | 7.3 | 9.0 | 3.4 | 7.2 | 4.20 | 112 | <0.001 |
| Days of problems with others | 2.2 | 6.2 | 1.3 | 4.6 | 1.42 | 112 | n.s. |
| Psychiatric composite | 0.3 | 0.2 | 0.2 | 0.2 | 2.73 | 106 | <0.01 |

[a] Composite scores calculated according to the model presented by P.L. McGahan et al. (unpublished). The measures cover the 30 days before the interview.

[b] $50 incremental change per unit.

[c] Higher scores indicate less severity.

used hallucinogens, 12% (N=15) had used amphetamines, and 7% (N=9) or fewer had used any of a number of other illicit drugs (heroin, methadone, other opiates, sedatives, barbiturates, PCP, inhalants, methaqualone) three or more times a week for at least a month. Almost four-fifths (79%, N=96) had received no previous treatment for drug use.

The follow-up group resembled the baseline group closely in terms of number of therapy sessions received. Over one-third received no therapy sessions (i.e., they dropped out of the study after one or two pretreatment research interviews) in both the baseline group (47%, N=79) and the follow-up group (41%, N=50). Thirty-three percent of the follow-up group (N=40) and 31% of the baseline group (N=52) dropped out between the first and fifth therapy sessions, and 26% of the follow-up group (N=32) and 22% of the baseline group (N=37) attended six or more sessions. The most common reasons given by patients in the follow-up interview for dropping out of treatment were conflicts with work, family, school, or finances (23%, N=28), conflicts within themselves about quitting cocaine use (23%, N=28), and wanting to quit in their own way or with the help of their families (20%, N=24). Of the 122 persons who were interviewed at follow-up, 50% (N=61) sought other treatment after their contact with our center. The most frequently sought types of further treatment were residential treatment (43%, N=52) and Narcotics Anonymous or Cocaine Anonymous (38%, N=46). Among the 61 people who sought treatment elsewhere, only 30 actually received such treatment. We are uncertain about exactly how much treatment they obtained, but no relationship between abstention from cocaine and receiving additional treatment was found.

### *Cocaine Use*

For many subjects, cocaine use in the follow-up period was episodic and could not be characterized easily by the variables used in our quantitative analyses. Therefore, it is worthwhile to provide a qualitative analysis of cocaine use during follow-up before discussing the quantitative findings. Detailed descriptions of the ups and downs of cocaine use were obtained in response to the open-ended question, "How has your drug use been since you were last at [the treatment center]?" For some of the subjects who were difficult to locate at follow-up, additional information was obtained through telephone conversations with the subject's families. A sampling of these accounts follows:

> My use got worse, I'd be up for 6 days straight, sleep when I blacked out, wake up, and start smoking again. This went on for 3 months. I stopped for a month, and now it's worse again.
>
> Before I used often, two to three times a week, with 1- to 2-day binges. Now I use once or twice a month. I snap out of it quick. No more binges. I wouldn't do it if I weren't exposed to temptation.
>
> I was not ready for treatment at the time of initial contact. My use later got out of control, and I spent all of my money. I entered residential treatment about 5 months after my initial contact with you. I am still using cocaine, but much less frequently now.
>
> [from wife] Things got worse for a while. His use depended on the money he had. When he had less money

**TABLE 3. Addiction Severity Index Scores Before and After Once-a-Week Psychological Treatment of Cocaine Abusers N=115[a]) Who Attended Fewer Than Six Sessions and Those Who Attended Six or More Sessions**

| Addiction Severity Index Measure[b] | Fewer Than Six Sessions (N=83) |  |  |  | Six or More Sessions (N=32) |  |  |  | ANCOVA[c] |  |
|---|---|---|---|---|---|---|---|---|---|---|
|  | Baseline |  | Follow-Up |  | Baseline |  | Follow-Up |  |  |  |
|  | Mean | SD | Mean | SD | Mean | SD | Mean | SD | F | df |
| Drug composite | 0.2 | 0.1 | 0.1 | 0.1 | 0.2 | 0.1 | 0.1 | 0.1 | 1.72 | 1, 102 |
| Days of cocaine use | 12.4 | 9.4 | 6.4 | 9.4 | 9.7 | 8.7 | 3.2 | 5.8 | 2.15 | 1, 106 |
| Days of marijuana use | 4.2 | 7.6 | 2.0 | 4.5 | 6.1 | 9.2 | 2.6 | 5.9 | 0.06 | 1, 106 |
| Dollars[d] spent on drugs | 8.4 | 6.6 | 2.6 | 3.9 | 8.7 | 7.2 | 3.2 | 5.7 | 0.55 | 1, 106 |
| Days of drug problems | 14.0 | 12.3 | 8.0 | 11.4 | 12.9 | 11.8 | 5.0 | 9.8 | 1.25 | 1, 106 |
| Alcohol composite | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.87 | 1, 106 |
| Days of alcohol use | 1.1 | 4.0 | 2.4 | 4.0 | 0.9 | 2.1 | 1.0 | 1.8 | 2.46 | 1, 106 |
| Dollars[d] spent on alcohol | 1.0 | 1.3 | 0.8 | 0.8 | 1.7 | 3.3 | 0.7 | 0.5 | 0.57 | 1, 106 |
| Days of alcohol problems | 0.3 | 2.2 | 0.8 | 4.1 | 1.0 | 5.4 | 0.4 | 1.3 | 0.19 | 1, 106 |
| Medical composite | 0.2 | 0.3 | 0.1 | 0.2 | 0.1 | 0.3 | 0.1 | 0.2 | 0.45 | 1, 103 |
| Days of medical problems | 2.7 | 6.5 | 2.3 | 5.5 | 3.1 | 7.9 | 2.0 | 4.3 | 0.46 | 1, 104 |
| Employment composite | 0.6 | 0.3 | 0.6 | 0.3 | 0.6 | 0.3 | 0.5 | 0.3 | 2.30 | 1, 99 |
| Days worked[e] | 14.6 | 11.4 | 12.1 | 10.6 | 14.0 | 12.9 | 14.8 | 11.2 | 2.02 | 1, 106 |
| Dollars[d] earned[e] | 12.2 | 9.1 | 9.9 | 8.9 | 11.1 | 9.9 | 12.3 | 8.9 | 2.78[f] | 1, 104 |
| Legal composite | 0.1 | 0.2 | 0.1 | 0.1 | 0.1 | 0.1 | 0.0 | 0.1 | 0.41 | 1, 97 |
| Days of criminal activity | 0.9 | 3.7 | 0.2 | 1.1 | 0.1 | 0.4 | 0.1 | 0.7 | 0.11 | 1, 104 |
| Family/social composite | 0.4 | 0.2 | 0.3 | 0.2 | 0.4 | 0.2 | 0.2 | 0.2 | 3.27[f] | 1, 97 |
| Days of problems with family | 7.4 | 9.4 | 3.4 | 7.4 | 7.0 | 8.2 | 2.9 | 6.6 | 0.08 | 1, 105 |
| Days of problems with others | 1.6 | 4.6 | 1.1 | 3.8 | 3.7 | 9.2 | 0.8 | 3.6 | 0.99 | 1, 105 |
| Psychiatric composite | 0.3 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.3 | 0.13 | 1, 99 |

[a] Seven patients were referred out before treatment and therefore were excluded from this analysis.

[b] Composite scores calculated according to the model presented by P.L. McGahan et al. (unpublished). The measures cover the 30 days before the interview.

[c] Conducted on follow-up scores by using pretreatment scores as covariates.

[d] \$50 incremental change per unit.

[e] Higher scores indicate less severity.

[f] $p<0.10$.

> because he was not working, he used less. While he was working he had lots of binges. He went to [Narcotics Anonymous] but not regularly. He entered an inpatient program a few months ago. He is expected to stay there for about a year.
>
> Use has increased slowly. I would like more treatment.
>
> [from wife] He had been in [a residential treatment setting] for a few months after leaving the therapy center. He had stopped using and was doing well. The program was supposed to send him to another facility in [another state], but at the last minute they were unable to do so. He came home about 2 months ago and started using crack because of his disappointment. Eventually he became abusive to me and the children. He refused my suggestion that he seek further treatment. Therefore, I asked him to leave the home, and he is now living on the streets.

Although these ups and downs characterized some persons, 19% of the group (N=23) had stopped using cocaine or crack for 3 or more months at follow-up. A conservative measure of abstinence from cocaine use was developed by combining self-report of cocaine use during an extended period with the results of urine testing at the time of follow-up. To qualify as abstinent, the subject had to have a negative urine test result and to report no use of cocaine in the prior 3 months (and, as a reliability test, no use of cocaine in the past 30 days). For the patients who were not able to report to our site for a urine test, the criteria were a self-report of no cocaine use in the prior 6 months and confirmation of nonuse by a special follow-up telephone call to a member of the patient's family. Using this conservative definition, we found 23 subjects to be abstinent and 90 to be abusing, and we could not determine the status of nine subjects.

### *Other Problems*

The baseline and follow-up scores on the Addiction Severity Index are shown in table 2. Drug use was significantly lower in the follow-up period than it was at the time of initial contact. The composite drug score was significantly lower in the 30 days preceding the follow-up interview, as were the number of days of cocaine use, the number of days of marijuana use, the amount spent on drugs, and the number of days of drug problems. Psychiatric/psychological problems, as indicated by the psychiatric severity score, were also significantly less serious at follow-up, and there was also a significant decline in family/social problems.

Although the alcohol composite score, the amount spent on alcohol, and the number of days of alcohol problems were almost unchanged, the number of days of alcohol use in the past 30 days increased significantly between intake and follow-up. Although superficially this might suggest that drug substitution was

**TABLE 4. Addiction Severity Index Scores Before and After Once-a-Week Psychosocial Treatment of Cocaine Abusers (N=113$^{a}$) Who Were or Were Not Abstinent at Follow-Up**

| Addiction Severity Index Measure$^{b}$ | Abstinent (N=23) | | | | Not Abstinent (N=90) | | | | ANCOVA$^{c}$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | Follow-Up | | Baseline | | Follow-Up | | | | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | F | df | p |
| Drug composite | 0.2 | 0.1 | 0.0 | 0.0 | 0.2 | 0.1 | 0.1 | 0.1 | 36.12 | 1, 105 | <0.001 |
| Days of cocaine use | 10.0 | 8.9 | 0.0 | 0.0 | 12.2 | 9.2 | 7.3 | 9.1 | 13.32 | 1, 108 | <0.001 |
| Days of marijuana use | 5.0 | 8.6 | 0.7 | 2.1 | 5.0 | 8.2 | 2.6 | 5.3 | 3.29 | 1, 108 | n.s. |
| Dollars$^{d}$ spent on drugs | 8.1 | 7.2 | 0.1 | 0.3 | 8.9 | 6.8 | 3.8 | 4.8 | 11.74 | 1, 107 | 0.001 |
| Days of drug problems | 16.0 | 11.8 | 0.3 | 1.5 | 14.2 | 12.6 | 9.6 | 11.8 | 15.23 | 1, 108 | <0.001 |
| Alcohol composite | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 1.18 | 1, 107 | n.a. |
| Days of alcohol use | 0.5 | 1.2 | 1.4 | 3.7 | 1.3 | 4.0 | 2.2 | 3.6 | 0.69 | 1, 108 | n.s. |
| Dollars$^{d}$ spent on alcohol | 0.7 | 0.6 | 0.6 | 0.5 | 1.4 | 2.3 | 0.9 | 1.1 | 1.12 | 1, 108 | n.s. |
| Days of alcohol problems | 0.8 | 4.0 | 0.0 | 0.2 | 0.5 | 3.2 | 0.9 | 3.9 | 0.92 | 1, 108 | n.s. |
| Medical composite | 0.2 | 0.3 | 0.1 | 0.3 | 0.1 | 0.2 | 0.1 | 0.2 | 0.02 | 1, 105 | n.s. |
| Days of medical problems | 2.6 | 5.3 | 3.2 | 7.1 | 2.5 | 6.7 | 1.9 | 4.5 | 1.45 | 1, 106 | n.s. |
| Employment composite | 0.6 | 0.4 | 0.5 | 0.3 | 0.6 | 0.3 | 0.6 | 0.3 | 3.45 | 1, 99 | n.s. |
| Days worked$^{e}$ | 13.8 | 13.1 | 14.8 | 11.2 | 13.9 | 11.5 | 12.0 | 10.6 | 1.21 | 1, 108 | n.s. |
| Dollars$^{d}$ earned$^{e}$ | 10.0 | 9.8 | 12.1 | 8.8 | 12.0 | 9.2 | 9.7 | 8.9 | 2.07 | 1, 106 | n.s. |
| Legal composite | 0.0 | 0.0 | 0.0 | 0.0 | 0.1 | 0.2 | 0.1 | 0.1 | 1.63 | 1, 97 | n.s. |
| Days of criminal activity | 0.2 | 0.8 | 0.0 | 0.0 | 0.8 | 3.6 | 0.3 | 1.1 | 0.93 | 1, 103 | n.s. |
| Family/social composite | 0.4 | 0.2 | 0.1 | 0.2 | 0.4 | 0.2 | 0.3 | 0.2 | 10.14 | 1, 98 | <0.01 |
| Days of problems with family | 7.7 | 8.2 | 0.5 | 1.0 | 7.7 | 9.4 | 4.3 | 7.9 | 5.73 | 1, 106 | <0.05 |
| Days of problems with others | 1.3 | 3.5 | 1.9 | 6.5 | 2.5 | 6.9 | 1.2 | 4.0 | 0.70 | 1, 106 | n.s. |
| Psychiatric composite | 0.3 | 0.2 | 0.1 | 0.1 | 0.3 | 0.2 | 0.2 | 0.3 | 4.84 | 1, 100 | <0.05 |

[a] Status of nine patients could not be determined.

[b] Composite scores calculated according to the model presented by P.L. McGahan et al. (unpublished). The measures cover the 30 days before the interview.

[c] Conducted on follow-up scores by using pretreatment scores as covariates.

[d] $50 incremental change per unit.

[e] Higher scores indicate less severity.

taking place, a more refined examination of the relationship between alcohol problems and length of abstinence from cocaine or crack showed that more of the subjects who had alcohol problems at follow-up, compared to those who did not, were also using cocaine or crack at follow-up ($r=-0.22$, $df=117$, $p<0.01$). This suggests that alcohol and cocaine are used together or that cocaine use is followed by alcohol intake in an attempt to reduce the excitatory effects of cocaine; such patterns are consistent with clinical reports. There were no changes between intake and follow-up in medical, employment, or legal problems.

### *Effect of Treatment*

We found only a suggestion, but no convincing evidence, that the treatment delivered in this study was responsible for the improvements seen. We reached this conclusion primarily because the number of sessions received was not significantly related to the number of days of cocaine use or to improvement in other scores. When we compared the subjects who had no therapy sessions with those who had 13 or more sessions, the same absence of a relationship between cocaine use and number of therapy sessions was found. However, nearly significant associations in the data suggested that the income increased and the family/social composite score improved for those persons who had six or more sessions as compared to those who had less treatment (table 3).

### *Relation of Cocaine Use to Other Problems*

As expected, the persons who were abstinent (had negative urine test results and reported no use of cocaine or crack for 3 or more months before the follow-up interview) had lower scores on both the drug composite index and on various individual drug items than did those who were still using cocaine (see table 4). This group also showed significantly more improvement in family/social and psychiatric areas than was seen among those who continued to use cocaine. However, no significant differences were seen between abstainers and continuing users in alcohol, medical, employment, and legal problems. Thus, there was a clear relationship between continuation of cocaine use and problems in several important areas of daily life.

## DISCUSSION

This study of 122 persons 6 to 12 months after initial treatment contact indicates that cocaine use disorder has a complex course, as does abuse of opiates or cigarettes (18). Fewer than 20% of the subjects on whom we had follow-up data had abstained from crack or cocaine use for at least 3 months in the follow-up period. The remaining persons either used it continuously after the first treatment contact or stopped and started periodically. Many of those who continued to use cocaine or crack applied to other treatment centers one or more times. A significant improvement in both psychological functioning (as indicated by the Addiction Severity Index psychiatric severity score) and family/social functioning was noted for the group as a whole. However, those who were not using cocaine at follow-up (19% of the cohort) accounted for virtually all of this improvement. This suggests that, in many areas associated with problems during cocaine use, improvement is directly tied to abstinence.

The close association between cocaine or crack use and the psychiatric composite score of the Addiction Severity Index is noteworthy. It confirms the previous finding (19) that use of cocaine produces or exacerbates symptoms of psychiatric disturbance. The subjects who were abstinent at follow-up and those who were not had similar scores at initial treatment contact, and a dramatic decline in scores was noted only among the persons not currently using cocaine; the scores of those who continued to use cocaine either remained unchanged or actually increased from entry to follow-up.

The finding of no association between number of treatment sessions and improved outcome is at variance with the results of studies that have shown a relationship between amount of treatment received and outcome after treatment of substance use disorders (20). Studies of psychotherapy (21) and family therapy (22) for heroin addicts receiving methadone maintenance treatment have shown treatment effects, but both studies offered therapy in addition to methadone, drug counseling, supervised urine testing, rules, and other structures offered by the treatment program. A number of clinicians working with cocaine addicts have reported success with a more intensive approach, in which group therapy, education, and individual or family therapy are delivered to drug-free patients in three to five 2–6-hour sessions per week for the first 4–8 weeks of outpatient contact (23–25). Less intensive treatment, as was offered in our study, was reserved for follow-up treatment of those who responded to the initial, more intense phase. The need for a more intensive initial phase of treatment is suggested by the fact that many of the patients who entered our study later sought residential treatment in other settings.

Future studies could explore the relationship between patient characteristics and treatment structure, intensity, and outcome for those with cocaine use disorders. The pharmacotherapies now available for cocaine use disorders could be important adjuncts. Such therapies may lower the high dropout rate seen here or may permit better results with a less intensive psychological component.

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# Risk Factors for Needle Sharing Among Methadone-Treated Patients

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*Objective: This paper examines the sociodemographic and psychiatric characteristics of patients taking methadone who continue to share needles. Method: Three hundred twenty-three patients were recruited from four methadone programs. Data were collected by using questionnaires and interviews. Psychiatric symptoms were measured with the SCL-90, the Beck Depression Inventory, and the Addiction Severity Index. Results: Twenty percent of these subjects reported sharing needles within the previous 6 months. Those who shared reported greater difficulty in acquiring new needles, more legal difficulties, more severe drug problems, and higher levels of psychiatric symptoms. Conclusions: These data suggest that patients who continue to share needles are a more disturbed subgroup of the methadone maintenance population. Efforts designed to reduce needle sharing may need to be more sharply focused on patients who are at greatest risk of infection, and these patients may require more intensive psychiatric services.*

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The role played by intravenous drug users in the spread of AIDS has gained considerable public, political, and scientific attention. This is due in large part to the growing number of confirmed AIDS cases that have been related either directly or indirectly to needle sharing. Intravenous drug use is the second greatest risk factor among all confirmed AIDS cases in the United States, and in some geographic areas it is the leading factor (1, 2). Additionally, in 1988 55% of the persons who became infected as a result of heterosexual activity were the sexual partners of intravenous drug users, and 70% of all children infected through perinatal transmission had mothers who were intravenous drug users or the sexual partners of intravenous users (2).

Because of the slow progression of AIDS, data on its prevalence document the consequences of past needle sharing and unprotected sexual contact. Current evidence suggests that the time between exposure to the virus and the development of AIDS will exceed 7 years for the majority of intravenous drug users (3 and presentations by F. Aiuti et al. and J.R. Robertson et al. at the Sixth International Conference on AIDS, San Francisco, June 20–24, 1990). Thus, even the most current AIDS case reports reflect high-risk behavior that may have occurred many years earlier.

In contrast to AIDS prevalence reports, studies of HIV infection rates provide insight into more recent high-risk behavior. In the United States, such studies have shown seropositivity ranging from less than 5% to over 60%, with considerable variation by regions of the country, by cities within regions, by neighborhoods within cities, and by involvement in treatment within neighborhoods (4–7).

While information from AIDS and HIV prevalence studies is important, such studies are also limited in their ability to provide specific information about persons presently at risk. In this regard, perhaps the most important factor contributing to the AIDS epidemic among intravenous drug users is their current needle sharing. Although it is not unrelated, this current practice cannot be determined from AIDS case data or studies of HIV infection alone. Even in areas with low rates of infection and few confirmed AIDS cases, needle sharing can be quite common, providing an opportunity for rapid transmission of the virus. Thus, the future course of the epidemic among intravenous drug

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users can be best understood by examining current needle-sharing practices.

This article describes the characteristics of patients treated with methadone who share needles. This patient population provided an opportunity to study a group of intravenous drug users who, by virtue of their treatment status, had increased access to AIDS information, drug counseling, methadone, and other related resources. By studying needle sharing within this context, we hoped to identify the individual characteristics associated with continued needle sharing. In particular we were interested in determining whether this high-risk behavior is related to knowledge of how the virus is transmitted, to fear of contracting AIDS, or to other demographic, social, or psychological characteristics.

## METHOD

The data were collected from 323 subjects participating in an ongoing study of the effectiveness of methadone treatment. All subjects were volunteers selected through extensive recruitment activities in four outpatient methadone treatment programs located in Philadelphia and New Jersey. The mean±SD age of the group was 38±7.2 years; 70% (N=227) were male. Whites and blacks were equally represented, with each accounting for 47% (N=153) of the total; Hispanics accounted for the remainder of the sample (5%, N=17). Self-reported drug use during the previous month was common. Forty percent (N=124) of those responding to this question reported using heroin at least once, 47% (N=150) reported using cocaine, and 51% (N=163) reported benzodiazepine use, primarily unprescribed. These figures reflect a significantly lower rate of drug use than that found among a comparable group of opiate addicts not in treatment (presentation by D.S. Metzger et al. at the Sixth International Conference on AIDS, San Francisco, June 20–24, 1990).

The study group represented approximately 35% of the average daily census of the methadone programs. Two procedures were implemented to assess the representativeness of the sample. After the subjects were enrolled in the study, their characteristics were examined by the staff from each of the participating programs. These reviews identified no obvious sampling bias. Statistical analyses of the characteristics of the sample and the available characteristics of all patients admitted to methadone treatment in the city of Philadelphia during the study's recruitment phase were also performed. These analyses found no differences in gender, race, high school graduation rate, or employment status. Thus, given the relatively large sample size, the multisite recruitment strategy, the staff reviews, and the statistical comparisons, we have confidence that the sample adequately represented the patient population from which it was drawn.

After they had given informed consent, the subjects were divided into groups of six to 10 and asked to fill out comprehensive risk assessment questionnaires. These data collection sessions were closely supervised by research staff members who were present to answer questions, assist those with reading difficulty, and screen questionnaires for missing data. The questionnaire assessed demographic information, treatment history, knowledge of ways in which AIDS is transmitted, drug use patterns, arrests and illegal activities, needle use, and fear of infection. Current psychological symptoms were measured with the SCL-90 (8) and the Beck Depression Inventory (9). Forty percent (N=128) of the 323 subjects were randomly selected and invited to participate in a personal interview that included the Addiction Severity Index (10), a structured interview which assesses the need for treatment in seven problem areas: medical, family/social, legal, employment, drug, alcohol, and psychiatric.

We examined variables from these measures as they relate to the high-risk practice of needle sharing. All analyses were conducted with the Statistical Package for the Social Sciences (11). It is important to note that these analyses were exploratory and were intended to generate specific hypotheses to be tested in prospective studies, which are currently underway.

## RESULTS

Respondents were classified into three risk groups on the basis of their reported needle use during the preceding 6 months. Of the 323 subjects, 38% (N=123) reported that they had not injected drugs, 42% (N=135) indicated that they had injected drugs but had not shared needles, and 20% (N=65) reported that they had injected drugs and shared needles at least once. These overall rates were compared across programs, and although rates of sharing varied from a low of 15% to a high of 26%, the interprogram differences were not significant ($\chi^2=3.67$, df=6, n.s.).

The three risk groups differed significantly only in race ($\chi^2=13.62$, df=4, $p<0.05$). Needle sharing was reported at a higher rate among whites (25%, N=38) and Hispanics (35%, N=6) than among blacks (14%, N=21). These three needle-sharing groups were equivalent on all other demographic variables. No differences in age or level of education were found. In all three risk groups about 70% of the subjects were unemployed. A somewhat higher proportion of men (21%, N=48) than women (18%, N=17) reported sharing needles, but this difference was not significant.

Respondents were asked to indicate the frequency of their use of heroin, cocaine, amphetamines, benzodiazepines (diazepam and alprazolam), marijuana, and alcohol during the month preceding assessment. Since the rate of use of the drugs commonly administered by injection in this population (heroin and cocaine) was quite low among those not injecting, tests of significance were performed in which only the two needle-using groups were compared. No significant differences in the frequency of use of any drugs except benzodiazepines were identified (table 1). The needle-

**TABLE 1. Frequency of Drug Use During the Preceding Month by Needle-Using Subjects Who Shared or Did Not Share Needles**

| Drug and Frequency of Use | Subjects Not Sharing Needles N[a] | Subjects Not Sharing Needles % | Subjects Sharing Needles N[b] | Subjects Sharing Needles % | $\chi^2$ (df=3) |
|---|---|---|---|---|---|
| Heroin | | | | | 1.24 |
| Daily | 4 | 2.9 | 2 | 3.3 | |
| A few times a week | 21 | 15.4 | 9 | 14.8 | |
| A few times a month | 54 | 39.7 | 29 | 47.5 | |
| Not at all | 57 | 41.9 | 21 | 34.4 | |
| Cocaine | | | | | 0.83 |
| Daily | 12 | 8.9 | 6 | 9.7 | |
| A few times a week | 26 | 19.3 | 15 | 24.2 | |
| A few times a month | 49 | 36.3 | 22 | 35.5 | |
| Not at all | 48 | 35.6 | 19 | 30.6 | |
| Benzodiazepines | | | | | 11.16[c] |
| Daily | 14 | 10.2 | 16 | 25.4 | |
| A few times a week | 15 | 10.9 | 11 | 17.5 | |
| A few times a month | 39 | 28.5 | 15 | 23.8 | |
| Not at all | 69 | 50.4 | 21 | 33.3 | |
| Marijuana | | | | | 1.64 |
| Daily | 4 | 2.9 | 2 | 3.2 | |
| A few times a week | 10 | 7.3 | 4 | 6.3 | |
| A few times a month | 30 | 21.9 | 19 | 30.2 | |
| Not at all | 93 | 67.9 | 38 | 60.3 | |
| Alcohol | | | | | 2.30 |
| Daily | 8 | 5.8 | 6 | 9.5 | |
| A few times a week | 17 | 12.4 | 10 | 15.9 | |
| A few times a month | 39 | 28.5 | 20 | 31.7 | |
| Not at all | 73 | 53.3 | 27 | 42.9 | |

[a] Total N for each drug varied from 135 to 137.
[b] Total N for each drug varied from 61 to 63.
[c] With the Bonferroni method, $p<0.05$.

**TABLE 2. Psychiatric Symptom Scores of 323 Drug-Using Subjects Divided According to Their Method of Drug Intake**

| Measure | Score: Subjects Not Injecting Drugs (N=123) | Score: Subjects Not Sharing Needles (N=135) | Score: Subjects Sharing Needles (N=65) | F (df=2, 308) |
|---|---|---|---|---|
| Beck Depression Inventory | 13.15 | 14.42 | 20.03 | 8.96[a,b] |
| SCL-90 scale | | | | |
| Somatization | 0.7987 | 0.7635 | 1.2800 | 9.06[b] |
| Obsessive-compulsive | 0.8099 | 0.7915 | 1.4525 | 13.82[b] |
| Interpersonal sensitivity | 0.6706 | 0.6981 | 1.2951 | 14.04[b] |
| Depression | 0.9107 | 0.9872 | 1.7285 | 17.99[b] |
| Anxiety | 0.6655 | 0.6572 | 1.3425 | 16.60[b] |
| Hostility | 0.6487 | 0.6593 | 1.4483 | 20.43[b] |
| Phobic anxiety | 0.3855 | 0.4119 | 0.6978 | 3.83 |
| Paranoid ideation | 0.6883 | 0.7206 | 1.4000 | 16.18[b] |
| Psychoticism | 0.4879 | 0.4508 | 0.9360 | 11.18[b] |
| General symptom inventory | 0.6350 | 0.6928 | 1.2608 | 15.13[b] |

[a] df=2, 313.
[b] Score of needle-sharing subjects significantly higher than scores of the other two groups, $p<0.01$ with the Bonferroni method.

sharing group reported significantly higher rates of benzodiazepine use. Forty-three percent (N=27) of the needle-sharing group reported use of diazepam and alprazolam a few times a week or every day, more than twice the rate reported by those not sharing needles.

Subjects were also asked about their access to new needles. Interestingly, the degree of difficulty in acquiring new needles differed significantly ($\chi^2=21.54$, df=2, $p<0.001$) among the three risk groups. Overall, 19% (N=38) of the 199 subjects who had injected drugs and who answered this question indicated that it was difficult to get new needles. Of the 135 who had injected but not shared, only 10% (N=14) found it difficult to get new needles. The rate was nearly four times greater (38%, N=24) for the 63 respondents who had injected and shared.

There were no differences in the length of time that the three risk groups had been in their current treatment programs (33 months). The groups did not differ with regard to number of past entries into treatment or current methadone dosage. Overall, the mean±SD daily methadone dose was 44±20 mg.

Members of the three risk groups were compared on their knowledge of effective ways to prevent HIV transmission. Consistent with previous findings, knowledge of preventive measures was widespread and did not differ significantly among the risk groups. The most frequently cited methods were "don't share needles or inject" (88%) and "use condoms" (68%).

Subjects were asked to indicate how worried they were 1) about getting AIDS and 2) that they had already been exposed to the AIDS virus. There was no significant difference among the three risk groups in the degree of fear of contracting AIDS. Sixty-nine percent (N=45) of the needle-sharing group, 57% (N=70) of the noninjecting group, and 56% (N=76) of the injecting group were at least moderately concerned about becoming infected. The three groups were also compared regarding their fear that they might already have been exposed to HIV; significantly more concern was expressed among respondents to this question in the needle-sharing group (57%, N=35) than in the no-injection group (32%, N=38) and the no-sharing group (31%, N=42) ($\chi^2=23.28$, df=8, $p<0.01$).

During the 6 months preceding our assessment, the needle-sharing group had been arrested significantly more often (F=3.6, df=2, 317, $p<0.05$) than the other two groups. Considering all charges, the average number of arrests per group was 0.13 for those who had not injected drugs, 0.18 for those who had injected drugs but not shared needles, and 0.35 for those who had shared needles. Despite this difference in arrest rates, subjects in the three groups did not differ with regard to the amount of time they had been incarcerated.

Psychological symptoms were significantly associated with needle sharing (table 2). The differences in Beck Depression Inventory scores not only were statistically significant but also represented clinically important differences. Similarly, significant differences in scores on each of the subscales of the SCL-90 were

**TABLE 3. Composite Scores From the Addiction Severity Index of 128 Drug-Using Subjects Divided According to Their Method of Drug Intake**

| | Score | | | |
|---|---|---|---|---|
| Problem | Subjects Not Injecting Drugs (N=48) | Subjects Not Sharing Needles (N=58) | Subjects Sharing Needles (N=22) | F (df= 2, 125) |
| Medical | 0.36 | 0.29 | 0.43 | 0.29 |
| Employment | 0.73 | 0.79 | 0.73 | 0.79 |
| Alcohol | 0.09 | 0.12 | 0.07 | 0.32 |
| Drug | 0.18 | 0.28 | 0.34 | 14.05[a] |
| Legal | 0.04 | 0.09 | 0.18 | 4.23 |
| Family/social | 0.16 | 0.23 | 0.34 | 4.24 |
| Psychiatric | 0.21 | 0.25 | 0.45 | 9.54[a] |

[a] Score of needle-sharing subjects significantly higher than scores of the other two groups, $p<0.05$ with the Bonferroni method.

found (table 2), again indicating significantly higher symptom levels in the group that shared needles. The other two groups (noninjectors and nonsharing injectors) did not differ significantly. In order to make corrections for the use of repeated univariate tests of significance, critical values for significance were adjusted by using the Bonferroni method (12). Even with this more stringent criterion of significance, scores on all but the phobic anxiety subscale were found to be significantly higher for the needle-sharing group than for the other two groups.

As can be seen in table 3, the data produced by the Addiction Severity Index were quite similar to those obtained from the questionnaire. The needle-sharing group had higher composite scores on the legal and family/social sections. They also had higher composite drug scores, reflecting a higher frequency of drug use, use of multiple substances, and higher severity ratings of problems associated with drug use. The composite scores on psychiatric problems were consistent with those on the SCL-90 and the Beck inventory: the Addiction Severity Index identified higher levels of psychiatric disturbance among the needle-sharing group. Composite scores for employment, alcohol, and medical problems did not differ among the three risk groups. When levels of significance for results of these tests were adjusted with the Bonferroni method, the group differences in the composite scores for the legal and family/social sections of the Addiction Severity Index were no longer significant, while the drug and psychiatric scores remained significantly different.

## DISCUSSION

The question we asked in these preliminary analyses was, Which methadone patients continue to share needles in the midst of the AIDS epidemic? The answers that emerged identified characteristics associated with recent needle sharing that may be important for understanding continued high-risk behavior. These characteristics included more arrests and legal difficulties, more severe drug problems, higher levels of psychiatric symptoms, and greater difficulty in obtaining new needles. All but the last of these characteristics are similar to those of patients classified in earlier studies as having severe psychiatric problems (13–15). When considered together, these characteristics describe a group of patients that may require more aggressive interventions than are generally available in methadone programs.

Contrary to our expectations, fear of AIDS was not associated with safer injection practices. Thus, our findings do not support the notion that reductions in needle sharing can be achieved by increasing the fear of infection, at least among this methadone-treated group. Perhaps most important, knowledge of methods of self-protection from infection was also not found to relate to needle sharing. As reported by others (16–18 and presentations by J.K. Watters and by J. Jackson and L. Rotkiewicz at the Third International Conference on AIDS, Washington, D.C., June 1987), such knowledge was nearly universal among the study group. Thus, for many of these subjects, awareness of risk coupled with knowledge about means of avoiding infection was not sufficient to eliminate needle sharing.

The relationship between restricted access to new needles and needle sharing is also noteworthy. Only a small part of this sample (12%, N=38) reported difficulty in obtaining new needles, yet among those who did, needle sharing occurred at a significantly higher rate. This finding supports the proposition that greater access to new needles might help reduce sharing among a small but potentially important group of intravenous drug users.

The association between psychological distress and recent needle sharing is particularly important. The SCL-90, the Beck inventory, and the Addiction Severity Index each indicated that the subjects who had shared needles within the preceding 6 months had significantly more psychiatric symptoms than those who had not shared. Regardless of the direction of the causal relationship between psychological distress and AIDS risk behavior, the strength of their association suggests that psychological factors need to be addressed in working with this high-risk population. Reduction of psychiatric symptoms may play an effective role in changing high-risk behavior.

The finding that patients with psychiatric symptoms were more likely to share needles is not surprising. In the past, higher levels of depression and anxiety have been associated with poor treatment outcome and relapse (13, 19, 20). Our data may merely reflect the limited ability of methadone treatment programs to have an impact on individuals with higher levels of psychological disturbance. However, with the exception of benzodiazepine use, treatment failure as measured by continued drug use was not related to needle sharing. Of course, high levels of psychiatric symptoms may also reflect the AIDS disease process itself. It is possible that the needle-sharing group included a higher proportion of individuals who were currently infected with HIV. Given the potential neurotropic effects of HIV, the higher level of psychiatric symptoms may have been indicative of early HIV infection. Our studies were not able to include serological or neuropsychological testing, but such assessments are necessary to address this question adequately, and they are currently underway.

These data suggest that in the midst of the AIDS epidemic, it is not sufficient for methadone programs simply to identify continued drug use. Increased monitoring of needle sharing and other high-risk behavior is demanded. Program staff members must be trained to discuss use of needles, methods of injection, and cleaning of injection equipment as an extension of their current response to identified drug use. This may pose a dilemma for some treatment personnel who feel that open discussion of these issues is an endorsement of drug use. However, we feel that such discussions are an essential component of drug counseling and may, in fact, provide further opportunities for effective interventions.

In this regard it must be noted that our subjects may have felt comfortable reporting needle sharing to the research staff because of the protection of confidentiality afforded by the research protocol. It is not clear whether patients will be equally open in discussing needle use with treatment staff members. The ability to discuss and change needle sharing and other high-risk behavior is probably a function of the counselor-patient relationship and program policies. The importance of this issue demands that programs develop and encourage counseling skills that will allow all high-risk behavior to be openly discussed. Program policies that will allow staff members to explore these areas without mandated punitive sanctions are also needed.

As we have demonstrated, elevated levels of psychiatric symptoms are associated with continued needle sharing among drug abuse patients in treatment. The higher level of symptoms may be the result of high-risk behavior, or it may be the force behind the high-risk behavior. In either case, our findings suggest that it may be possible to identify methadone-treated patients who are at relatively greater risk for HIV infection. Our findings also suggest that the behavior of patients who continue to share needles may be particularly intractable and will most likely require the establishment of additional psychiatric services within treatment programs. Involvement in methadone treatment is an important first step in AIDS risk reduction, but it may not be sufficient for the more disturbed and perhaps antisocial subgroups. Methadone programs will probably need to expand and intensify services in order to address the needs of those patients who continue to be most at risk for becoming infected and for spreading the infection to others.

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# Implications of Self-Reported Cognitive and Motor Dysfunction in HIV-Positive Patients

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*Objective: The authors examined HIV-positive subjects to determine the relationship of patient complaints of cognitive and motor dysfunction to psychiatric status and performance on established cognitive and motor function tests. Method: HIV-positive volunteers (N=77) were evaluated at entry into a longitudinal neurological study. Forty were asymptomatic, 29 had AIDS-related complex, and eight had AIDS. The subjects were not selected for the presence or absence of cognitive or motor complaints. Complaints of cognitive and motor dysfunction were assessed with items from the AIDS Clinical Trials Group Macro Neurologic Exam. Current depression and anxiety were assessed with the Profile of Mood States. Psychiatric status was assessed with the NIMH Diagnostic Interview Schedule, a structured interview that provides* DSM-III *psychiatric diagnoses. Actual cognitive and motor performance was measured with standard neuropsychological tests known to be sensitive to the effects of HIV. Results: Cognitive complaints were found in 38 (49%) of the subjects. These complaints were associated with psychiatric symptoms but not with cognitive performance. Motor complaints, found in 12 (16%) of the subjects, were associated with poorer motor performance but not with psychiatric symptoms. The overall frequency of psychiatric diagnosis was high. Conclusions: Self-reports of cognitive and motor dysfunction were common in this unselected group and are of concern to health care providers. Potentially treatable psychiatric conditions were also common, particularly in subjects with cognitive complaints, and appropriate treatment referrals are indicated. Patients who report motor dysfunction should be neurologically evaluated for treatable causes.*

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It is now well established that HIV can cause dementia in the later stages of the disease process, even in the absence of opportunistic infections. This syndrome, which has been called the AIDS dementia complex, is characterized by slow mental processing, forgetfulness, apathy, gait instability, and slow motor functioning (1). The prevalence of mild cognitive impairment in the early stages of the disease is still controversial (2).

The conventional wisdom about other dementias is that many patients who report memory loss are depressed but not demented and that many truly demented patients do not complain of memory loss (3, 4). We investigated the relationship between patient complaints, psychiatric status, and measured cognitive and motor performance in a group of HIV-positive patients.

## METHOD

The subjects were 77 HIV-positive volunteers evaluated at entry into a longitudinal neurological study. Our recruitment sources were clinics for infectious diseases and hemophilia, statewide HIV support groups, newspaper articles, and word of mouth. The subjects were not selected for the presence or absence of cognitive or motor complaints. Their risk factors for HIV were homosexual contact (N=59), exposure to blood products (N=7), heterosexual contact (N=3), intravenous drug use (N=1), and combinations of these risk

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factors (N=7). Most subjects were male (N=71) and white (N=60). The group's characteristics were similar to national AIDS statistics except for underrepresentation of intravenous drug users and nonwhites (5). The mean±SD age was 33.5±8.3, and the average educational level was 13.4±3.3 years. Forty (52%) of the subjects were asymptomatic (CDC stage II or III), 29 (38%) had AIDS-related complex (ARC) (CDC stage IVa), and eight (10%) had AIDS (CDC stage IVb, IVc, or IVd). The subjects were carefully evaluated for factors other than HIV that can negatively affect neuropsychological performance, i.e., preexisting developmental, neurologic, and psychiatric diagnoses, past and current substance abuse, and limited formal education (6).

Patient complaints of cognitive dysfunction were assessed with the four "cognitive function/elicited complaints" items from the AIDS Clinical Trials Group Macro Neurologic Exam, developed by R. Price and J. Sidtis (NIH protocol ATEU 005). Each patient was asked about his or her perception of problems related to concentration and speed of thought, reading or watching television, memory, and speech. On the basis of the patient's self-report, each of the four items was rated by the interviewer on a 5-point scale ranging from normal (score=0) to severe impairment (score=4). All items include specific criteria for each point on the scale. For example, the memory complaints range from "mildly more forgetful than usual, will occasionally miss appointments" (rated as 1) to "persistently disoriented to time, frequently to place or person" (rated as 4). The scores for the four cognitive function/elicited complaints items were summed for each subject to yield an overall measure of self-reported cognitive dysfunction. Motor complaints were similarly assessed with four interview items related to gait, arm coordination, involuntary movement, and bladder incontinence.

Although the elicited complaints items cover a limited number of symptoms, they have been specifically chosen to address important features of the AIDS dementia complex (1). An item was not rated if its evaluation was precluded by extraneous factors, such as orthopedic disease. Each interview and rating was completed by a neurologist (C.R.S. or C.D.H.) who was blind to the patient's neuropsychological and psychiatric test scores.

Current levels of depression and anxiety were assessed with the depression/dejection and tension/anxiety scales of the Profile of Mood States (POMS) (7). The POMS is a paper-and-pencil self-report measure; for each item the patient indicates on a 5-point scale the extent to which an adjective describes feelings experienced during the past week. The scores for the items are summed to yield an overall score for each measure, and higher scores indicate greater distress.

Each patient was administered the NIMH Diagnostic Interview Schedule (DIS) (8), a structured 60–90-minute interview that provides lifetime and current psychiatric diagnoses based on *DSM-III* criteria. The subjects were classified dichotomously for the presence or absence of the following psychiatric diagnoses within the past 6 months: schizophrenia, bipolar disorder, major depression, posttraumatic stress disorder, generalized anxiety disorder, panic disorder, and alcohol or drug abuse or dependence.

Actual cognitive and motor performance was measured with a battery of standard neuropsychological tests (4). The cognitive tests included measures requiring rapid visual-motor integration and alternation between stimulus sets (WAIS-R Digit Symbol, Trail Making Test), which have been found to be sensitive to the effects of HIV (1). Additional cognitive tests were measures of confrontational naming (Boston Naming Test) and memory (Rey Auditory Verbal Learning Test; Rey Complex Figure delayed recall; Wechsler Memory Scale logical memory and visual reproduction, Russell procedure). Motor functioning was assessed with timed tests of gross and fine motor speed that are sensitive to the motor effects of HIV (Timed Gait, Lafayette Grooved Pegboard, Finger Tapping) (1).

The subjects were classified dichotomously for the presence or absence of cognitive impairment relative to published norms. Subjects were classified as cognitively impaired if their scores fell below the cutoffs on two or more of 10 cognitive measures. The 10th percentile was used as the cutoff for the WAIS-R Digit Symbol, Trail Making Test parts A and B, Boston Naming Test, Rey Auditory Verbal Learning Test five-trial average, Rey Complex Figure delayed recall, and Wechsler Memory Scale logical memory immediate and delayed recall. A Russell rating of 3 or worse was the criterion for the Wechsler Memory Scale visual reproduction immediate and delayed recall. The subjects were also classified dichotomously for the presence or absence of motor impairment relative to published norms. They were classified as impaired if their scores fell below/above the following cutoffs on one or more of five motor measures: more than 12.5 seconds for Timed Gait, below the 10th percentile for the Lafayette Grooved Pegboard test for dominant and nondominant hands, and a Russell rating of 3 or worse for Finger Tapping for dominant and nondominant hands. Two subjects with preexisting severe ambulatory problems due to hemophilia were not classified as having motor impairment because their only low motor score was on Timed Gait. Additional information on the published norms used is available on request.

Pearson product moment correlations were computed for continuous variables. Chi-square analyses were used for categorical variables.

## RESULTS

Of the 77 subjects, 38 (49%) reported some decline from baseline cognitive functioning and 12 (16%) reported a decline from baseline motor functioning. There was little correlation between the patients' self-reports of cognitive dysfunction and their performance on the neuropsychological tests. Only the Digit Symbol score was significantly correlated with complaints of cognitive impairment ($r=-0.27$, $df=76$, $p=0.02$). However, there were significant correlations between these self-reports and levels of depression ($r=0.46$, $df=67$, $p=0.0001$) and anxiety ($r=0.49$, $df=67$, $p=0.0001$). Partial correlations with education did not substantially change these findings.

The patients with cognitive complaints did not have a significantly higher prevalence of cognitive impairment, according to neuropsychological testing, than those without such complaints ($\chi^2=1.60$, $df=1$, $p>0.05$). They did, however, have a significantly higher prevalence of psychiatric disorders within the past 6 months ($\chi^2=6.01$, $df=1$, $p=0.01$).

In contrast, there were significant correlations between self-reported motor impairment and lower performance on four of the five measures of gross and fine motor function (Timed Gait: $r=0.53$, $df=67$, $p=0.0001$; Grooved Pegboard dominant hand: $r=0.56$, $df=76$, $p=0.0001$; Grooved Pegboard nondominant hand: $r=0.43$, $df=74$, $p=0.0001$; Finger Tapping dominant hand: $r=-0.21$, $df=75$, $p>0.05$; Finger Tapping nondominant hand: $r=-0.25$, $df=73$, $p=0.03$). There were nonsignificant correlations between these self-reports and levels of depression and anxiety. Partial correlations with education weakened but did not eliminate the significant correlations between complaints and poorer motor performance, suggesting that more educated subjects are more accurate self-observers.

Furthermore, significantly more patients with motor complaints, compared to patients without them, were classified as having motor impairment on the basis of neuropsychological testing ($\chi^2=4.89$, $df=1$, $p=0.03$). There was no significant difference in the prevalence of psychiatric disorders in the past 6 months ($\chi^2=3.15$, $df=1$, $p>0.05$).

The frequency of psychiatric diagnosis in these unselected subjects was striking. Of the 38 subjects with cognitive complaints, 31 (82%) met the *DSM-III* criteria for one or more of the following psychiatric diagnoses in the past 6 months: major depression (N=20), posttraumatic stress disorder (N=7), bipolar or atypical bipolar disorder (N=4), schizophrenia (N=3), alcohol abuse or dependence (N=3), drug abuse or dependence (N=3), generalized anxiety disorder (N=3), and panic disorder (N=3). It should be noted that psychiatric symptoms in this group were not always manifested as cognitive concerns. Of the 39 subjects without cognitive complaints, 23 (59%) also met the criteria for psychiatric disorders in the past 6 months: major depression (N=18), alcohol abuse or dependence (N=4), posttraumatic stress disorder (N=3), generalized anxiety disorder (N=2), and panic disorder (N=1).

The rates of cognitive impairment according to formal neuropsychological testing were 30% for the asymptomatic patients, 34% for the patients with ARC, and 75% for the patients with AIDS. The rates of motor impairment were 23%, 28%, and 88%, respectively. However, these impairments were not necessarily all attributable to HIV. We have written elsewhere (6) about the marked prevalence of such confounding factors as preexisting neurologic, developmental, and psychiatric diagnoses in our unselected subjects and the importance of considering them before attributing low test scores to HIV.

## DISCUSSION

Complaints of cognitive and motor dysfunction were common in this unselected group of HIV-positive volunteers. Such complaints are of concern to health care providers who must recommend appropriate treatments. It is important to rule out treatable opportunistic infections, and primary neurological complications may respond to zidovudine (9). Our results demonstrate that there is also a striking frequency of potentially treatable psychiatric conditions in HIV-positive individuals, particularly those with complaints of cognitive dysfunction. Appropriate referrals for treatment should be provided. Our findings do not, of course, indicate that patients who report cognitive dysfunction never have cognitive deficits. Motor complaints were associated with poorer motor performance, and patients who report motor dysfunction should be neurologically evaluated for treatable causes.

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# Expenditures for Psychotropic Medications in the United States in 1985

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*Objective: Psychotropic medications have seldom been included in estimates of the costs of mental health services. In the infrequent case that these costs have been assessed, they have been estimated by using national surveys of consumers of health services. The objective of this study was to estimate the costs of prescriptions for psychotropic medications in the United States in 1985 and to assess the difference with the most recent cost estimate from a health services survey (1977). Method: Study data were based on retail costs of psychotropic medications reported to the Pharmaceutical Data Service Alpha National Prescription and Sales Audit. The data come from a computerized survey panel of 2,250 pharmacies representative of the more than 14,000 pharmacies nationwide. The database includes all medication prescriptions filled, whether paid with cash or Medicaid or reimbursed by third-party payment. Analyses were limited to psychotropic medication prescriptions. Results: In 1985, $1.45 billion was spent on outpatient psychotropic medications. Nearly $868 million (60% of the total) was spent on antianxiety and sedative-hypnotic medications, while approximately $263 million (18%) was spent on antipsychotic medications, $240 million (17%) on antidepressants, and $84 million (5%) on combination psychotropic medications. These expenditures were much higher than would have been expected given the most recent health services estimate of $513 million. Conclusions: These results demonstrate the substantial cost of psychotropic medications in 1985. The finding that the cost of psychotropic medications was so high, in contrast to the lower estimate from the 1977 survey, demonstrates the importance of obtaining more frequent cost estimates and basing future estimates on medication databases.*

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Psychotropic drugs are widely used in the United States. In a community-based study conducted in 1979 (1), 17% of respondents reported using a psychotropic medication during the previous year. A 1980–1981 survey of physician prescriptions in outpatient settings (2, 3) estimated a total of 56.8 million physician visits in which a psychotropic drug was prescribed. The majority of psychotropic prescriptions were by primary care physicians (66.0%), with psychiatrists prescribing only 17.2% and other medical specialists the remaining 16.8%. These findings were replicated with the 1985 National Ambulatory Medical Care Survey (3, 4).

Psychotropic medications are common therapies within both mental health and general health care. Although significant costs are thought to accompany the prescribing of psychotropic drugs, little information exists on total national expenditures for these medications. Baum et al. (5) used prescription patterns to estimate that psychotropic medications were the third most frequently prescribed class of drugs, representing about 9% of all prescriptions in 1984. These authors did not, however, convert their prescription data into cost estimates.

The importance of accurately estimating expenditures on psychotropic medications is increased by a number of factors. Currently, regulations for psychotropic drugs are being considered and implemented to contain inappropriate use of psychotropic drugs and perceived excess expenditures (6). Efforts to finance medical management of mental disorders (7) could benefit from accurate cost estimates. In addition, the

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effects of new, expensive drugs such as clozapine (8, 9) cannot be accurately assessed without baseline estimates. Accurate estimates of the national cost of psychotropic medications are required both by policy makers and by mental health service researchers.

The only previous source of data concerning national expenditures for psychotropic medications that were not limited to individuals with psychiatric diagnoses has been the 1977 National Medical Care Expenditures Survey, which was based on a random selection of households in the civilian, noninstitutionalized U.S. population. Cafferata and Kasper (10) completed a study of psychotropic medications that was based on data from the 1977 survey and reported findings very similar to those of the study by Baum and colleagues (5), with 9.2% of the 900 million prescriptions in 1977 for psychotropic medications.

Unlike Baum et al. (5), Cafferata and Kasper (10) took their analyses one step further, calculating that $513 million was spent on psychotropics in 1977. This estimate was recognized for its importance and was later referenced and used by Frank and Kamlet (11) in estimating mental health care costs and expenditures in the United States in 1985.

Although the 1977 study provided one of the few estimates of the cost of psychotropic medications, it has several limitations beyond being, at last publication, more than a decade out of date. First, psychotropic services and costs were a secondary feature of that survey. In addition, the collection of data relied upon the recollection of respondents and their ability or willingness to report accurate information.

Researchers have demonstrated that reservations about psychotropic drug treatment are common among the general public (12). Respondents may have been reluctant to report medications obtained through nonmedical channels, e.g., those borrowed from a friend or relative, which were reported to constitute a small but significant proportion—3.1%—of all psychotropic medications used in the United States in 1979 (1).

More direct sources of data on expenditures for psychotropic medications are the commercial databases used for pharmaceutical marketing research. Two prominent pharmaceutical databases are the National Prescription Audit, maintained by IMS America Ltd., and the Alpha National Prescription and Sales Audit, maintained by Pharmaceutical Data Services, Inc. These databases provide analytic potential for more accurate estimates of psychotropic drug use in the United States. (Readers who wish further information should contact Michael I. Smith, Ph.D., Pharmaceutical Data Services, Inc., 9060 East Via Linda, Scottsdale, AZ 85258-5499.) Baum et al. (5) analyzed 1984 data from IMS America to find a total of 131 million prescriptions for psychotropic medications that can be grouped into four different classes: minor tranquilizers (71 million), major tranquilizers (21 million), antidepressants (cyclic and combination drugs for anxiety and depression) (34 million), and other psychotropic medications (including monoamine oxidase inhibitors, lithium, and analeptics) (5 million).

The 131 million prescriptions in 1984 represent a 58% increase over the estimate from the 1977 study by the National Medical Care Expenditures Survey. As further evidence of the underestimate associated with the 1977 study, Baum et al. (5) provided data from 1975 through 1984 which indicated that the number of prescriptions for psychotropic medications in 1984 was estimated to be less than the 1977 number.

The large discrepancy between the estimates by IMS America and the National Medical Care Expenditures Survey for the total number of prescriptions for psychotropic medications nationwide could be due to the accuracy of the different methods that the two studies used to collect data. In particular, by directly obtaining data on all prescriptions filled, the IMS study eliminated problems with responder recall. Therefore, it is important to develop convergent validity of estimates by using alternative, yet comparable, databases. Thus, the present study analyzed the 1985 data sets of Pharmaceutical Data Services in order to provide information about the national cost of psychotropic drugs according to clinical drug categories.

## METHOD

The cost data analyzed in this study were derived from retail costs reported to the Alpha National Prescription and Sales Audit (13), a pharmaceutical marketing database maintained by Pharmaceutical Data Services. Since 1981 the Alpha National Prescription and Sales Audit has been compiled from monthly data tapes obtained from a survey panel of 2,250 computerized pharmacies. These stores are selected to be representative of the over 14,000 pharmacies nationwide that report data to the Pharmaceutical Data Services. Pharmacies report all prescriptions filled on every business day including transactions involving cash, Medicaid, and prescriptions reimbursed by third-party payment. Forty percent of these pharmacies are "chain," and 60% are independent. Other outlets, such as discount stores and supermarkets with pharmacies, are not included in this sample. Hospital and nursing home pharmacies also are not included

Although the panel of pharmacies is not a true random sample, the stratified sample frame does ensure that the panel is representative of U.S. pharmacies in terms of region (nine geographic regions are used), type of ownership, and size (13). The 2,250 selected stores report four million prescriptions each month and are selected from a representative sample of pharmacies that provide more than 40% of all prescriptions filled in the United States each day. The database combines individual drugs into therapeutic groups according to the Uniform System of Classification (14). For the purposes of this study, drugs were regrouped into clinical psychiatric categories. Sedative-hypnotic drugs, which are not considered to be a psychotropic

**TABLE 1. Estimated Expenditures for Outpatient Purchases of Psychotropic Drugs in the United States in 1985**

| Category and Drug | Expenditure[a] (thousands of dollars) |
|---|---|
| I: Antianxiety and sedative-hypnotic | $ 867,272 |
| Benzodiazepines: antianxiety | 707,461 |
| Long half-life | 360,569 |
| Short and medium half-life | 346,892 |
| Benzodiazepines: sedative-hypnotic | 75,460 |
| Hydroxyzine | 49,325 |
| Addictive sedative hypnotics | 26,228 |
| Meprobamate | 8,134 |
| Not identified | 664 |
| II: Antidepressant | 239,755 |
| Tricyclic antidepressants | 175,806 |
| Tertiary amines | 119,264 |
| Secondary amines | 56,542 |
| New antidepressants | 57,967 |
| MAO inhibitors | 5,755 |
| Not identified | 227 |
| III: Antipsychotic | 262,616 |
| Phenothiazines | 146,845 |
| Piperazines | 87,602 |
| Piperidines | 46,708 |
| Aliphatics | 12,535 |
| Haloperidol | 64,777 |
| Thioxanthenes | 25,474 |
| Loxapine | 9,528 |
| Molindone | 1,375 |
| Lithium | 14,278 |
| Not identified | 339 |
| Combinations of drugs from categories I, II, and III | 83,632 |
| Total | 1,453,275 |

[a]Data from the Alpha National Prescription and Sales Audit.

medication according to the Uniform System of Classification, were included in the present analysis.

## RESULTS

The data on expenditures for psychotropic drugs for 1985 are presented in table 1. During that year $1.45 billion±SD $21.0 million was paid out for psychotropic drugs for ambulatory care. This total represents a 183% increase from Frank and Kamlet's high estimate of expenditures for psychotropic medication for 1980 (11) and a 449% increase from their low estimate for that year. Even when inflation is taken into account, this estimate is $500 million greater than their high 1980 estimate.

Over three times as much money was spent on the anxiolytic and sedative-hypnotic drugs of category I as was spent on either the antidepressants in category II or the antipsychotic medications in category III. The last two were approximately the same in total expenditures.

Ninety percent of the money spent on category I psychotropic drugs was used to purchase benzodiazepines. A roughly equal amount was expended on the long half-life and the short and medium half-life anxiolytic benzodiazepines. Another $80±$1.2 million was spent on long half-life benzodiazepines prescribed as sedative-hypnotics. A total of $34±$0.49 million was used to purchase the older and potentially more harmful category I drugs, such as the barbiturates, glutethimide, ethchlorynol, and meprobamate.

Almost three-quarters of the money spent on the antidepressant drugs (category II) was spent on the tricyclic antidepressants. Twice as much was spent on the older-generation tertiary amine tricyclics as was spent on the newer-generation secondary amine tricyclics.

The third major category of psychotropic drugs, antipsychotic medications (category III), included neuroleptic medications and lithium. Over half of the total expenditures for these drugs were for phenothiazines; the first-generation aliphatic phenothiazines accounted for about 9% of the total for this class. More recently developed antipsychotics such as the butyrophenones (i.e., haloperidol), the thioxanthenes, the dibenzoxapines (i.e., loxapine), and the dihydroindolones (i.e., molindone) accounted for about 39% of the total amount spent on antipsychotic medication.

## DISCUSSION

The present results indicate a much higher cost of psychotropic medications than indicated by the 1977 study by the National Medical Care Expenditures Survey (10). The $1.45 billion estimate for 1985 is nearly triple the earlier estimate. No more than one-third of this difference may be attributable to inflation. In addition, the increase from the 1977 estimate may be due partially to increased utilization between 1980 and 1985. Baum et al. (5) had estimated that psychotropic prescriptions had increased approximately 9% from 1980 to 1984, while Larson et al. (3) had found that they had increased 11% during the period 1980–1981. Regardless, inflation and increased use cannot fully account for the substantial discrepancy between estimates. It is likely that the present strategy for estimating the national costs of psychotropic medications is more accurate in that the Pharmaceutical Data Services does not require self-reporting by consumers.

There are several notable limitations to the present study. First, the sample is not a true random sample. However, the sample of stores on which the database is developed is representative and probably constitutes the best available sample. It is noteworthy that grocery or discount store pharmacies are not included. Although the percent of market share of prescriptions held by these stores is not known, their absence from the IMS America database could lead to an underestimation of the total costs of psychotropic medications. In addition, the present estimates are only for drugs for ambulatory use. The absence of hospital and nursing homes leads to an underestimate of the total national expenditures for psychotropic medications.

The majority of expenditures for psychotropic medications is on antianxiety compounds. This suggests a potential area for cost-containment initiatives. In particular, studies have shown that these drugs are given chronically and in doses that are too high, especially to elderly patients (15). A fairly substantial amount of money, $34 million, went for the purchase of outdated and potentially more harmful medications like the barbiturates and meprobamate. While these compounds may be used for the treatment of epilepsy, the large expenditures found suggest an area for future investigation.

Within the antidepressant medications, the tricyclics dominate the market. Among antipsychotics, the phenothiazines still are the most commonly used. The changing patterns of antipsychotic drug use in the past decade from low-potency to high-potency neuroleptics (16) may partially account for the increased costs documented in 1985.

In sum, the present study reveals that approximately $1.45 billion was spent on psychotropic medications in 1985 for ambulatory care. This represents a far larger portion of total health care expenditures than previously estimated. Although further research is necessary to understand the relationship between prescribing patterns and clinical need, cost containment measures might usefully be directed toward those drugs with the largest expenditures.

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# Parents' Emotional Neglect and Overprotection According to the Recollections of Patients With Borderline Personality Disorder

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*Objective: The purpose of this study was to test clinical hypotheses about the role of emotional neglect and overprotection in the childhood of patients with borderline personality disorder. Method: The subjects were male and female borderline (N=62) and nonborderline (N=99) patients from a general hospital psychiatric clinic and a university student mental health clinic. Both groups were administered the Parental Bonding Instrument, which measures subjects' recollections of parenting on dimensions of care and protection. Results: The findings showed that the patients with borderline personality disorder remembered both their fathers and their mothers as having been significantly less caring and more controlling than did the nonborderline patients. The results were the same for male and female subjects and for subjects from both sites. Conclusions: The recollections provide support for psychodynamic theories about the childhood of borderline patients and for a theory of biparental failure in the development of borderline pathology.*

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Clinicians treating patients with borderline personality disorder have proposed that early family experience could contribute to the development of this disorder. Adler (1) suggested that the sense of aloneness felt by these patients could be accounted for by their parents' unavailability to them when they were children. Masterson and Rinsley (2) described pathological enmeshment in childhood, with overprotective mothers interfering with autonomous development. On the basis of the developmental theory of Mahler et al. (3), Masterson and Rinsley suggested that selective maternal availability during the separation-individuation phase of development predisposes to borderline psychopathology later in life. In this view the mother accepts the child's needs for symbiosis but rejects needs for autonomy. Consequently, one could conceptualize the ideas of Masterson and Rinsley about the childhood of patients with borderline personality disorder as combining elements of overprotection and neglect. This would explain the oscillations of attachment seen in borderline patients—oscillations between feelings of engulfment and feelings of abandonment by others (4).

These ideas have been empirically investigated both by asking patients to recollect their childhoods (5–9) and by directly observing families (10). The data suggest that patients with borderline personality disorder remember their childhoods as characterized by emotional neglect. The evidence on whether neglect was remembered in relation to fathers, mothers, or both parents has been somewhat contradictory. Although most data have not suggested that borderline patients remember their parents as overprotective (5, 7, 9), one study (8) reported recollections of both overprotection and neglect.

There are methodological problems with these studies. In several cases (5–7) the instruments used to measure childhood recollections of parental behavior lacked reliability and validity. Only two previous reports (8, 9) used a well-standardized measure, Parker's Parental Bonding Instrument. Some studies (5, 7, 9) used only female borderline patients, whereas others (6, 8) collapsed data from both male and female patients. Since the developmental path to psychopathology may be different in the two sexes, a study that allows separate analysis of reports from male and female subjects is needed. Also, some samples have been drawn from patients in hospital clinics (6, 8), whereas other studies have examined patients who are university students (5, 7, 9). A research design that allows comparison of patients drawn from different sites would be valuable, since the childhood experiences of borderline patients who reach the university level of

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**TABLE 1. Scores on the Parental Bonding Instrument of Male and Female Patients With and Without Borderline Personality Disorder From Two Sites**

| | Scores of Borderline Patients (N=62) | | | | | | | | Scores of Nonborderline Patients (N=99) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Male (N=28) | | | | Female (N=34) | | | | Male (N=45) | | | | Female (N=54) | | | |
| | University (N=10) | | Hospital (N=18) | | University (N=18) | | Hospital (N=16) | | University (N=20) | | Hospital (N=25) | | University (N=29) | | Hospital (N=25) | |
| Item | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Care[a] | | | | | | | | | | | | | | | | |
| Mother | 21.7 | 10.3 | 22.8 | 6.5 | 19.2 | 9.9 | 18.3 | 6.3 | 28.0 | 7.3 | 25.2 | 6.6 | 25.2 | 9.7 | 23.5 | 8.5 |
| Father | 16.2 | 5.3 | 15.3 | 7.3 | 18.1 | 8.3 | 20.2 | 8.6 | 24.2 | 9.4 | 17.4 | 7.8 | 22.1 | 9.1 | 21.6 | 11.9 |
| Protection[b] | | | | | | | | | | | | | | | | |
| Mother | 17.8 | 10.3 | 19.6 | 9.5 | 15.4 | 10.6 | 18.3 | 16.9 | 14.8 | 6.6 | 17.4 | 7.3 | 15.1 | 7.7 | 12.9 | 8.0 |
| Father | 17.8 | 7.5 | 18.8 | 9.8 | 13.6 | 7.2 | 10.0 | 7.9 | 10.5 | 6.2 | 14.4 | 7.8 | 15.0 | 8.8 | 12.6 | 7.6 |

[a] Four-way ANOVA: main effect for diagnostic groups (F=15.53, df=1, 153, p=0.0001).

[b] Four-way ANOVA: main effect for diagnostic groups (F=8.69, df=1, 153, p=0.004).

education could be different from those of patients who do not. Finally, the sample sizes in all of the previous studies were small, limiting the generalizability of the data. The present investigation used a well-validated instrument with a larger sample of patients with borderline personality disorder and included both male and female subjects drawn from university and hospital clinic populations.

## METHOD

Male and female subjects were drawn from two sites, a university student mental health service and a general hospital outpatient psychiatry clinic. Diagnoses were established by using the retrospective version of the Diagnostic Interview for Borderline Patients (DIB) (11). The retrospective version has been shown to be equivalent to the interview version for purposes of establishing a diagnosis of borderline personality disorder (12). Chart review was carried out for all subjects by a senior psychiatrist (J.P.) who was blind to other measures. Patients who received scores of 7 or more out of 10 on the DIB were included in the borderline group (N=62). Those who received scores of 4 or less were assigned to the nonborderline group (N=99). To ensure that two discrete groups were obtained, patients who received a score of 5 or 6 were excluded from the study. The mean±SD ages for the total borderline and nonborderline groups were 29.6±9.6 and 29.3±8.6 years, respectively (F=0.03, df=1, 153, n.s.). Both the borderline and the nonborderline subjects were subgrouped on the basis of sex and site. The subgroup of female university students was the same as that used in a previously published preliminary report (9). The number of patients in each subgroup is reported in table 1.

The Parental Bonding Instrument (13) was administered to all subjects. This is a self-report scale measuring perceptions of two dimensions (care and protection) underlying parental behavior. The care items range from affection to neglect. The protection items range from overprotection to allowance of independence. The instrument requires subjects to score their parents on a 4-point Likert scale (0–3) on 25 items (12 concerning care and 13 concerning protection) as remembered from their first 16 years. Scores for care (range=0–36) and protection (range=0–39) were obtained for each parent. The Parental Bonding Instrument has been standardized in a series of large-scale normative studies and has reasonable test-retest and split-half reliability (14). Tests for validity of the instrument in both normative and clinical populations showed concurrence with ratings of parental behavior made by siblings, with parents' self-ratings, and with clinical ratings drawn from interviews of subjects and their parents (14).

## RESULTS

The mean scores and standard deviations for care and protection for both borderline and nonborderline patients according to sex and site are presented in table 1. In order to investigate whether the Parental Bonding Instrument scores could be differentiated according to diagnostic group, sex of patient, or site, two four-way, mixed-design analyses of variance (ANOVAs) were carried out for both the care and protection scores with diagnostic group, sex of patient, and site as the three between-subject factors and sex of parent as the within-subject factor.

The ANOVA for care yielded a highly significant main effect for diagnostic group: the borderline patients remembered their parents as being less caring than did the nonborderline patients. Differences in the main effects of sex of patient and site did not reach significance. The only interaction that reached significance was Sex of Parent by Sex of Patient (F=8.36, df=1, 153, p=0.004). A post hoc Tukey test revealed that mothers were perceived as more caring than fathers by male patients only (p=0.01).

The ANOVA for protection also yielded a highly significant main effect for diagnostic group: the borderline patients remembered their parents as more protective than did the nonborderline patients. Differences in the main effects of sex of patient and site did not reach significance. A trend was obtained with respect to sex of parent: mothers were perceived as more protective than fathers (F=3.20, df=1, 153, p=0.08). None of the two-way or higher-order interactions was significant.

## DISCUSSION

The care scores on the Parental Bonding Instrument support earlier studies showing that borderline patients remember their parents as emotionally neglectful (5–9) and resolve earlier contradictions about whether neglect was perceived as coming from one parent (5) or both (6–9). Borderline patients in this study reported low levels of care from both mother and father. Assuming that the perceptions of our borderline patients were accurate, this failure of both parents is in accord with Adler's theory (1) that borderline patients experience an inadequate holding environment in childhood, which leads to affective instability and impulsivity later in life. The question of whether perceptions might be different for male and female patients was answered by our data, which showed that the male and female borderline patients had the same memories of their parents. This justifies combining data on male and female patients in future studies. The fact that the results were the same for university students and hospital clinic patients shows that the findings are not specific to any particular group of borderline patients.

The protection scores on the Parental Bonding Instrument, which show that the borderline patients remembered both parents as overprotective, contradict earlier studies (5–9) that failed to demonstrate significant differences between borderline patients and other patients on measures of overprotection. Three of these studies (5–7) did not use a well-validated measure of overprotection. In a previous study from our center that did use the Parental Bonding Instrument (9), we also did not find a difference in protection scores between borderline and nonborderline female university students. However, the means in table 1 show that by surveying patients of both sexes from two sites, we were able to detect a difference which had been obscured by studying female students only. The validity of this finding is supported by the fact that the means for our nonborderline group were very close to those reported for community samples (14), whereas our borderline patients had much higher protection scores than the community norms. In addition, our findings confirm those of another study in which the Parental Bonding Instrument was used (8). This provides empirical confirmation of the hypotheses advanced by Masterson and Rinsley (2) about the mothers of borderline patients.

When the results for both care and protection are combined, the recollections of the borderline patients conform to what Parker has termed "affectionless control," which is most strongly associated with depressive syndromes (14). This makes sense, since borderline patients have a high rate of comorbid affective disorder (15). Borderline patients are telling us that they remember their parents as both failing to provide basic emotional support and preventing them from separating. This suggests that the parents of borderline patients could have put their own emotional needs ahead of empathic responsiveness to their children.

The fact that affectionless control was recollected by borderline patients in relation to both of their parents is interesting in the light of theoretical speculations which have tended to focus exclusively on the role of the mother (1, 2). It is possible that the child who will become a patient with borderline personality disorder is unable to buffer negative experiences with one parent by positive experiences with the other.

The findings of this study can explain only some of the variance in the development of borderline personality disorder. Other reports, for example, have demonstrated a higher incidence of physical and sexual abuse in the histories of borderline patients (16, 17). Moreover, there is evidence for constitutional factors in the borderline syndrome (18).

The question of falsification must be considered in interpreting any study that uses a retrospective design. This is especially true for borderline patients, who tend to distort features of their interpersonal relationships (1). However, borderline patients have not uniformly described all aspects of their childhood experience as negative when wider surveys of their childhood memories have been done (7). Prospective studies or studies of high-risk subjects are needed (18). In spite of these limitations, the convergence of evidence from studies that have used different methods provides support for the validity of the findings. The evidence in this study supports a number of clinical impressions from psychotherapists and makes theoretical sense in accounting for some of the psychopathology seen in borderline patients.

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# Kleptomania: A Report of 20 Cases

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*Objective: The authors' objective was to provide phenomenologic, family history, and treatment response data on a group of rigorously diagnosed patients with kleptomania. Method: Twenty consecutive inpatients and outpatients met* DSM-III-R *criteria for current kleptomania or a past history of kleptomania. These patients were given structured diagnostic interviews, and their family histories of psychiatric disorders were assessed blindly. The patients' responses to psychosocial and biological treatments were also assessed. Results: All of the kleptomanic patients had lifetime diagnoses of major mood disorders, 16 had lifetime diagnoses of anxiety disorders, and 12 had lifetime diagnoses of eating disorders. A high morbid risk of major mood disorders (0.31) was found in their first-degree relatives. Ten of 18 patients receiving thymoleptic medications reported reduction or remission of their stealing behavior. Conclusions: Kleptomania may be related to major mood disorder and perhaps may represent another form of "affective spectrum disorder."*

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Kleptomania is defined in *DSM-III-R* as the recurrent failure to resist impulses to steal objects not needed for personal use or their monetary value. The stealing is often abrupt and without premeditation, collaboration with others, or full consideration of the likelihood of apprehension. However, kleptomanic stealing also resembles a classic compulsion in that the urge to steal is experienced as intrusive and senseless, with increasing anxiety or tension if the urge is resisted and tension relief when the act is completed. The stealing, therefore, is ego-dystonic (1). Indeed, although classified in *DSM-III-R* as an impulse control disorder, kleptomania has been hypothesized by some to be a variant of obsessive-compulsive disorder (2–4).

Little is known about kleptomania. In our recent review of the literature (5), we found no systematic studies of a series of rigorously diagnosed kleptomanic individuals. Therefore, to further characterize this disorder, we report here on the demographics, phenomenology, associated psychopathology, family histories, and treatment histories of 20 consecutive psychiatric patients meeting *DSM-III-R* criteria for kleptomania.

## METHOD

Twenty-eight patients with apparent kleptomania were recruited by asking clinicians at our hospital to refer to us all inpatients and outpatients with possible kleptomania. One of these patients was interviewed but excluded because her stealing was invariably premeditated and for personal gain rather than in response to irresistible urges and thus did not meet *DSM-III-R* criteria for kleptomania. Seven other patients were not interviewed because they refused (N=2), repeatedly missed interview appointments (N=3), or were too psychotic to be evaluated (N=2). The 20 patients who completed the interview are the subjects of this report.

After providing informed consent, the patients were given a structured questionnaire based on the *DSM-III-R* criteria for kleptomania (6); a semistructured interview to elicit demographic data and information about the phenomenology and course of kleptomania and the presence of other *DSM-III-R* impulse control disorders; and the Structured Clinical Interview for DSM-III-R (SCID) (7). All interviews were performed by one investigator (S.L.M.). Family histories were obtained by a second investigator (P.E.K.), who was blind to the patient's diagnosis. Morbid risk of major mood disorders in relatives was calculated as described elsewhere (8).

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**TABLE 1. Clinical Characteristics and Response to Thymoleptic Treatment of 20 Patients With Kleptomania**

| Patient | Age (years) | Sex | Duration of Illness (years) | Peak Frequency of Stealing (episodes/ month) | Items Stolen | Fate of Items Stolen | Thymoleptic Medication | Treatment Response[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | 30 | F | 3[b] | 30 | Food, clothes, jewelry, cosmetics | Used | Tranylcypromine<br>Fluoxetine plus lithium<br>Trazodone | None<br>None<br>Partial |
| 2 | 30 | F | 20 | <1 | Money, pens, clothes | Used | Imipramine plus lithium<br>Valproate | None<br>Remission (8 months) |
| 3 | 42 | M | 35 | 8 | Records, books, electronic components | Hoarded | Lithium | Remission (11 months) |
| 4 | 35 | F | 9[b] | 120 | Laxatives, pens, paper, toys, money | Used, given away | Imipramine<br>Tranylcypromine<br>Fluoxetine | None<br>None<br>None |
| 5 | 33 | M | 13 | 90 | Food, clothes, books, towels | Given away | Fluoxetine plus imipramine | Remission (7 months) |
| 6 | 29 | F | 9[b] | 30 | Food, gifts, toiletries, cosmetics | Used, hoarded, given away | Desipramine<br>Fluoxetine<br>Trazodone | None<br>None<br>None |
| 7 | 47 | F | 12[b] | 4 | Magazines, rubber gloves, paper cups, plastic bags, gauze | Used, hoarded | Fluoxetine | None |
| 8 | 36 | F | 31 | 30 | Money, candy, food, socks, cosmetics, jewelry, drugs, toiletries | Used, hoarded, given away, discarded | Fluoxetine | Remission (3 months) |
| 9 | 29 | F | 16 | 2 | Diet pills, laxatives | Used, discarded | Fluoxetine | Remission (11 months) |
| 10 | 45 | M | 36 | 30 | Pens, books, pornography, sporting equipment | Used, given away, discarded | —[c] | |
| 11 | 23 | F | 3 | 4 | Food, jewelry | Used | Tranylcypromine | None |
| 12 | 36 | F | 10[b] | 4 | Clothes, shoes, cosmetics, money, jewelry | Used | Fluoxetine<br>Clonazepam<br>Fluoxetine plus lithium | None<br>Partial<br>Partial |
| 13 | 47 | M | 18[b] | 1 | Books, food, clothes | Used, given away | Carbamazepine plus clomipramine | None |
| 14 | 36 | M | 23 | 2 | Records, shoes, toiletries | Used, given away | None | |
| 15 | 25 | F | 10[b] | 30 | Food, clothes, jewelry, tapes, sheet music, money | Used, given away | Fluoxetine | None |
| 16 | 48 | F | 38[b] | 90 | Food, tools, videotapes, clothes, toiletries, jewelry | Used, given away | Imipramine<br>Lithium<br>Fluoxetine | None<br>None<br>None |
| 17 | 45 | F | 3 | 8 | Food, toys, film, clothes, toiletries, cosmetics | Used, hoarded, given away | Nortriptyline | Remission (15 months) |
| 18 | 21 | F | 5 | 30 | Food, clothes | Used | Fluoxetine | Partial |
| 19 | 36 | F | 5 | 16 | Clothes, jewelry, cosmetics, accessories | Used, given away | Trazodone<br>Tranylcypromine | Remission (12 months)<br>None |
| 20 | 39 | F | 25[b] | 12 | Clothes, cameras, accessories | Used, given away | Imipramine<br>Fluoxetine<br>Tranylcypromine<br>Lithium | None<br>None<br>None<br>None |

[a] Duration of remission given in parentheses.
[b] Patient exhibited kleptomanic symptoms at the time of evaluation.
[c] Patient was not given drug while actively kleptomanic.

## RESULTS

The demographic and clinical features of the patients are given in table 1. Most (N=15) were women. The patients' mean±SD age was 36±8.0 years (range=21–48), their duration of illness was 16±11 years (range=3–38), and they had a peak frequency of stealing of 27±33 episodes/month (range=0.3–120). Three

**TABLE 2. Current and Lifetime *DSM-III-R* Diagnoses in 20 Patients With Kleptomania**

| | Number of Patients | |
|---|---|---|
| Diagnosis | Current Diagnosis | Lifetime Diagnosis |
| Mood disorders | 13 | 20 |
| Bipolar | 5 | 7 |
| Bipolar not otherwise specified | 4 | 5 |
| Major depression | 4 | 8 |
| Psychoactive substance use disorders[a] | 2 | 10 |
| Alcohol abuse or dependence | 2 | 9 |
| Amphetamine abuse or dependence | 0 | 2 |
| Cocaine abuse or dependence | 0 | 3 |
| Other substance abuse or dependence | 0 | 4 |
| Anxiety disorders[a] | — | 16 |
| Panic disorder with or without agoraphobia | 3 | 8 |
| Agoraphobia without panic | 1 | 1 |
| Social phobia | 4 | 8 |
| Simple phobia | 5 | 6 |
| Obsessive-compulsive disorder | 7 | 9 |
| Eating disorders[a] | 6 | 12 |
| Anorexia nervosa | 1 | 6 |
| Bulimia nervosa | 5 | 12 |
| Impulse control disorders[a] | 3 | 8 |
| Pathological gambling | 0 | 2 |
| Pyromania | 1 | 3 |
| Trichotillomania | 2 | 3 |
| Intermittent explosive disorder | 0 | 2 |
| Psychotic disorders | 0 | 0 |
| Antisocial personality disorder | 0 | 0 |

[a] Total is less than the sum of the individual disorders because many patients had more than one disorder in the category.

were inpatients at the time of evaluation, and another eight had had previous psychiatric hospitalizations. Nine reported active kleptomanic symptoms at the time of interview.

All patients described irresistible urges to steal and a reduction of anxiety or relief of tension either during or shortly after the act of theft, as required in *DSM-III-R*. Although many found the urges senseless, intrusive, and ego-dystonic, some reported pleasurable feelings during the act of theft, variously described as "a rush," "a thrill," "high," "euphoric," or "manic." All patients stated that they considered their stealing to be wrong, and most reported guilt or remorse after stealing. Some patients atoned for stealing by donating stolen goods to charity, returning to victimized stores to pay for stolen items or to purchase unneeded items, or calling stores to alert clerks of their stealing.

Most patients stole from retail stores. Some, however, stole from their work locations or from individuals, particularly family members. Several patients developed rules for their stealing behavior—for instance, stealing only from work or from certain types of stores (e.g., drug stores but not department stores), or stealing certain items but not others (e.g., jewelry but not clothing).

Fifteen of the patients were apprehended for stealing at least once (range=1–12 times). Three had gone to jail. All reported feeling extremely frightened and ashamed at the time of apprehension. However, apprehension and/or jail had varying effects on kleptomanic symptoms over the long-term. Five of the apprehended patients (none of whom was jailed) stopped stealing permanently, but eight experienced only a few weeks' or months' remission, and two experienced no lapse in their stealing at all.

Ten of the 20 patients reported a history of some stressful or traumatic event other than apprehension. These included physical or sexual assault, witnessing physical assault on a parent, witnessing the loss of a home in a fire, and involvement in a fatal car accident. These events occurred from 5 to 21 years before the onset of kleptomania in seven cases and 16–30 years after the onset of kleptomania in three cases. In other words, no patient appeared to develop kleptomanic symptoms as direct sequelae of a stressful or traumatic event.

Of 11 patients receiving psychotherapy while symptomatic, none reported reductions in their kleptomanic symptoms. By contrast, of 18 patients receiving treatment with thymoleptics (table 1), 10 described a partial or complete remission in stealing urges and behavior (one patient responded to two different agents). In several patients, kleptomanic symptoms recurred when medication was discontinued and remitted again when the drug was reinstituted.

When we looked at the associated current and lifetime psychiatric disorders noted in the SCID interviews, we found that all 20 patients met *DSM-III-R* criteria for at least one other psychiatric disorder, and 17 met criteria for four or more disorders (table 2). All had initially sought treatment for conditions other than kleptomania, particularly mood disorders (N=8), anxiety disorders (N=4), or eating disorders (N=8). Of note, many patients did not reveal their stealing to their treater until after apprehension or after kleptomanic symptoms had responded to treatment administered for a concurrent disorder. Many patients concealed their kleptomania from family members. Some patients, despite having other serious psychiatric disorders, claimed that their stealing was the most debilitating or humiliating of their symptoms.

All 20 patients met *DSM-III-R* criteria for a lifetime diagnosis of major mood disorder (table 2). The onset of mood disorder preceded onset of kleptomania by at least 1 year in 12 patients, occurred within the same year in three patients, and occurred after the onset of the kleptomania in five patients. Six patients had made at least one suicide attempt. Many patients noted a relationship between their affective and kleptomanic symptoms, including changes in the frequency of stealing when they were depressed or manic. Additionally, some patients reported that the rush or thrill experienced with stealing seemed to relieve their depressive and/or manic symptoms.

Other disorders often associated with kleptomania were bulimia nervosa with or without anorexia nervosa, obsessive-compulsive disorder, and alcohol abuse or dependence. Most of the bulimic patients stole food as well as items other than food.

Patients reported a variety of psychopathological symptoms, particularly compulsive behaviors not meeting *DSM-III-R* criteria for obsessive-compulsive disorder because of either the nature or the severity of the symptom. These included compulsive shopping, hoarding, giving away wanted or needed objects, picking of skin, exercising, and sexual activity. Several men but none of the women reported paraphilic symptoms (e.g., ego-dystonic urges to have sexual relations with children or sadistic sexual fantasies).

No patient met *DSM-III-R* criteria for antisocial personality disorder. Some patients, however, described isolated antisocial behaviors in addition to stealing. These included lying (six patients), fire setting (three patients), changing price tags (two patients), breaking and entering (two patients), vandalism as a child (one patient), forgery (one patient), driving while intoxicated (one patient), and physical assault of a husband by a wife (one patient). Of note, some of these associated antisocial behaviors appeared to be due to concurrent psychiatric diagnoses, specifically, pyromania (fire setting), alcohol dependence (driving while intoxicated), intermittent explosive disorder (physical assault), and kleptomania (breaking and entering, changing price tags, forgery, and lying). Patients were not systematically assessed for other axis II disorders.

The prevalence of psychiatric disorders among the first-degree relatives aged 16 years old and older of the 20 kleptomanic patients is presented in table 3. The morbid risk for major mood disorders among the first-degree relatives of the kleptomanic probands was 0.31, a figure similar to the 0.25 risk observed in an earlier study from our center, based on similar methodology, in the relatives of subjects with major depression (7). Of the 20 kleptomanic patients in the current study, 12 had at least one first-degree relative with a mood disorder. Fifteen patients had family histories of other major psychiatric disorders, and two patients had a first-degree relative with kleptomania.

## DISCUSSION

We assessed the demographics, phenomenology, course of illness, associated psychopathology, family histories of psychiatric disorders, and treatment histories of 20 patients meeting *DSM-III-R* criteria for kleptomania. All patients described recurrent, intrusive, and irresistible urges or impulses to steal. Some attempted to resist the urges at least part of the time; others did not, claiming that the urges were too compelling or overpowering. All patients believed that their stealing was wrong; most felt guilty, ashamed, and embarrassed about their behavior.

The most striking finding of this study was that all patients demonstrated substantial psychopathology in addition to kleptomania—most notably major mood disorder (in particular, bipolar disorder) but also anxiety disorders, alcohol and other psychoactive substance use, eating disorders, and other impulse control disorders. First-degree relatives of kleptomanic patients also displayed high rates of mood and other psychiatric disorders. By contrast, few patients displayed substantial antisocial behavior other than stealing, and none met *DSM-III-R* criteria for antisocial personality disorder.

**TABLE 3. Prevalence of Psychiatric Disorders in the First-Degree Relatives[a] of 20 Patients With Kleptomania**

| Disorder | Relatives Affected (N=103) N | % |
|---|---|---|
| Mood disorders | 22 | 21 |
| Bipolar disorder | 5 | 5 |
| Major depression | 17 | 17 |
| Alcohol and other psychoactive substance use disorders | 21 | 20 |
| Alcohol | 14 | 14 |
| Other | 7 | 7 |
| Anxiety disorders | 13 | 13 |
| Panic disorder and/or agoraphobia | 6 | 6 |
| Obsessive-compulsive disorder | 7 | 7 |
| Eating disorders | 3 | 3 |
| Anorexia nervosa | 1 | 1 |
| Bulimia nervosa | 2 | 2 |
| Kleptomania | 2 | 2 |
| Psychotic disorders | 0 | 0 |

[a] Aged 16 years and older.

These findings are affected by several methodological limitations, however. Most importantly, patients were recruited from psychiatric referrals, and this very likely led to higher rates of associated psychopathology in this group than among all kleptomanic individuals. In addition, interviews were performed by an investigator who was not blind to the subjects' diagnoses, and no comparison group was examined. Thus, the high rates of associated psychopathology found in this study might be largely attributable to the method of subject selection. A more accurate assessment of these rates can be obtained only by controlled studies using interviews of kleptomanic subjects recruited from community-based samples conducted by interviewers who are blind to the subjects' diagnoses.

Previous observations, nevertheless, have suggested that kleptomania may be related to major mood disorder. For example, high rates of associated affective symptoms have been reported among kleptomanic individuals (5), kleptomania has been reported to respond to treatment with antidepressants and ECT (9–14), and kleptomanic stealing has been reported to alleviate major depression (12, 13, 15–17). Moreover, kleptomania appears to be associated with eating disorders (5, 18–25), which, in turn, appear to be related to mood disorder on the basis of the phenomenology, course, family history, and response to thymoleptics (23, 26, 27).

The findings of this study further support the hypothesis that kleptomania is related to major mood disorder. All 20 of the patients in this study met *DSM-*

*III-R* criteria for a current or past major mood disorder, and a surprisingly large number of the patients exhibited bipolar disorder. Indeed, some patients claimed that the "rush" they experienced with stealing was similar to their hypomanic or manic episodes. These observations invite the speculation that there may be a particular link between kleptomania and bipolar disorder.

The phenomenologic similarity of kleptomanic stealing to the compulsive rituals of obsessive-compulsive disorder raises the possibility that the two disorders are related. Indeed, kleptomania could actually be diagnosed as obsessive-compulsive disorder under *DSM-III-R* were it not for the *DSM-III-R* requirement that obsessive-compulsive disorder cannot be diagnosed if the compulsive behavior is attributable to another disorder. This speculation is supported by the findings that nine of our 20 kleptomanic patients had a history of *DSM-III-R* obsessive-compulsive disorder and that an additional six displayed compulsive behaviors in addition to stealing.

The potential relationship of kleptomania to obsessive-compulsive disorder, eating disorders, and major mood disorder raises the possibility that all four of these diagnostic categories might represent members of an extended family of disorders—which we have previously termed affective spectrum disorder—linked by a common pathophysiological "step" critical to their expression (27). For instance, evidence from biochemical studies suggests that serotonin deficit states may play a role not only in the genesis of mood disorders (28), obsessive-compulsive disorder (29, 30), and bulimia nervosa (31) but also in the genesis of impulsive behavior in general (28, 32–37). It is tempting, therefore, to speculate that the common "step" might involve serotonin deficiency. An alternative explanation of the apparent efficacy of fluoxetine—a highly specific serotonin agonist—in some kleptomanic patients is that this drug possesses specific anti-impulsive effects in addition to its antidepressant and anti-obsessive effects. Further research will be required to test these hypotheses.

Finally, two theoretical criticisms of our findings should be addressed. First, many patients in this study group stole in a way that was more systematic or less impulsive than that specified by the *DSM-III-R* criteria for kleptomania. For instance, some stole items of substantial value, planned thefts, or used stolen items. However, all patients—even those who reported frequent "systematic" stealing—also reported many "pure" kleptomanic episodes of stealing unneeded objects in response to irresistible, senseless urges. To exclude those patients who displayed "systematic" stealing in addition to "pure" kleptomania might generate a skewed sample of kleptomanic individuals not fully representative of the disorder in general. Moreover, if these "systematic stealers" did not truly have kleptomania, one might expect that they would meet criteria for antisocial personality disorder and fail to respond to antidepressants—in contrast to what was actually observed.

A second theoretical criticism is that this study does not resolve the question of whether kleptomania is in fact a valid diagnostic entity. Kleptomania might, on the one hand, be a nonspecific behavior exhibited with elevated frequency by patients with depression—a behavior that declines when the underlying depression is treated with antidepressants. On the other hand, as others have argued, kleptomania (38, 39) and, perhaps, other compulsive behaviors (40) may be voluntary acts that should not legitimately be labeled as diseases at all. This latter hypothesis is difficult to reconcile with the observation that 10 of the 18 patients in this group treated with thymoleptics displayed a partial or complete remission of kleptomanic behavior.

In conclusion, kleptomania may represent an underdiagnosed disorder of substantial morbidity, probably displaying comorbidity with other major psychiatric disorders, particularly mood, obsessive-compulsive, and eating disorders. Further investigation into the phenomenology, course, and associated psychopathology of kleptomania, as well as studies of its prevalence, biology, and response to both psychosocial and pharmacological treatments would therefore appear warranted.

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# Hypnotically Induced Auditory Hallucinations and the Mouth-Opening Maneuver: A Failure to Duplicate Findings

Eugene E. Levitt, Ph.D., and Thomas G. Waldo

Objective: *The authors sought to replicate the part of a study by Bick and Kinsbourne in which hypnotically induced auditory hallucinations in normal volunteer subjects were abolished by requiring the subjects to open their mouths.* Method: *Sixty-four normal volunteer subjects were hypnotized, and an attempt was made to induce auditory hallucinations. The subjects in whom hallucinations were successfully induced were then asked to perform the mouth-opening maneuver and the control maneuvers of putting their fingers in their ears or squeezing their eyes shut in an effort to end the hallucinations.* Results: *Sixteen subjects reported having hallucinations. None of them reported that a hallucination was abolished by opening the mouth or closing the eyes; four reported ending hallucinations by putting their fingers in their ears.* Conclusions: *Opening the mouth does not affect auditory hallucinations induced by hypnosis in normal persons. The most likely reason for the discrepancy between the results of this experiment and those of the Bick and Kinsbourne study is that the design of the latter study was faulty because it permitted demand characteristics to influence the results.*

(Am J Psychiatry 1991; 148:658–660)

An experiment was conducted by Bick and Kinsbourne (1) in an effort to test the hypothesis that "auditory hallucinations may be projections of schizophrenic patients' verbal thoughts, subvocalized due to deficient cerebral cortical inhibition." The basic maneuver of the experiment was to attempt to obstruct the hypothesized subvocalization by requiring the hallucinating individual to open his or her mouth, which makes subvocalization impossible. Bick and Kinsbourne studied two groups of subjects: 18 schizophrenic inpatients and 21 normal volunteers who were college students. Our concern in this report is with the normal subjects.

Bick and Kinsbourne used two control maneuvers in addition to the mouth opening: 1) closing the eyes tightly and 2) making a tight fist. The experimenters stated that the three maneuvers were requested "in a random order, counterbalanced across subjects" for the schizophrenic subjects, and while this statement was not repeated with respect to the normal subjects, presumably it was applied to them as well. Since there are six possible permutations of the three maneuvers, there could have been three or four normal subjects in each order, but the experimenters did not comment on this. Nor is it known whether the subjects were hypnotized individually or by group according to the order in which the maneuvers were presented. Nothing was said about the technique for the induction of hypnosis or the precise wording of the suggestion to hallucinate. Because of these omissions, it is not possible to replicate exactly the normal-subject segment of the experiment.

In any event, some alteration in the authors' study design seemed warranted. Bick and Kinsbourne informed their subjects before the instructions for the maneuvers that they would later be asked to state "if your voices got worse, stayed the same, or went away." Such disclosure greatly magnifies the possibility that the results will be largely a function of the demand characteristics of the experiment. This possibility was further increased by the fact that two of the three maneuvers were relatively remote from the speaking-hearing axis.

The maneuver of making a tight fist seemed to us to be too remote from auditory hallucination, so we decided to substitute for it forefingers in the ears, which is closer to the speaking-hearing axis. Of course, if Bick and Kinsbourne's hypothesis is correct, the nature of the control maneuvers is irrelevant.

In addition to the high possibility that the results were affected by demand characteristics, we had an-

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other reason to doubt Bick and Kinsbourne's findings. According to their report, auditory hallucinations were induced in 60% (N=21) of their 35 normal subjects. No previously published report has ever given a proportion that high. The standardization data for the Stanford Hypnotic Susceptibility Scale, Form C (2), show that attempts to induce verbal auditory hallucinations were successful in only 9% of subjects. The standardization sample for the Stanford Profile Scales of Hypnotic Susceptibility (3) had a 23% success rate in attempts to induce a musical auditory hallucination.

Subjects scoring at the top of both the Stanford Hypnotic Susceptibility Scale, Form C, and the Harvard Group Scale of Hypnotic Susceptibility (4) are evidently the most highly susceptible subjects and therefore the most likely to experience hypnotically induced hallucinations. Kihlstrom and Evans (unpublished data, 1979) did not report scores by item, but their subjects with high scores on both scales constituted only 10% of their sample. In a similar investigation by Register and Kihlstrom (5), this figure was 15%.

Finally, Bick and Kinsbourne arranged the crucial chi-square of their table 1 incorrectly. The test for a difference between the successes of the fist and eye maneuvers compared to the mouth maneuver in abolishing hallucinations did not test the authors' hypothesis directly. All three maneuvers abolished the hallucinations for two subjects. This is a result not in accord with the hypothesis, so the results for these subjects belong with those of the three subjects whose hallucinations resisted all three maneuvers. The consequent chi-square, to which Yates' correction is properly applied, is 4.90, which is still significant (at the 0.05 level) but represents considerably less reliability than the chi-square of 34.52 ($p<0.0001$) reported by Bick and Kinsbourne.

## METHOD

For our study of auditory hallucinations, 64 normal volunteer subjects were recruited by means of notices on college campus bulletin boards. They were hypnotized in groups by using verbatim the induction technique of the Harvard Group Scale of Hypnotic Susceptibility (4). A nine-item version of the scale itself was then administered. All hypnotic sessions were carried out by the second author. The items eliminated from our version of the scale were head falling, posthypnotic suggestion, and amnesia. The experimenter then attempted to induce auditory hallucinations by giving the following suggestions.

> In a moment, I will give you a signal. When I do, listen carefully and you will hear a voice or voices that seem to come from an unknown source close to you. The voices will be speaking to you, but you may or may not always hear them clearly. Be sure you are listening carefully when I give the signal . . . . Ready, VOICES NOW! [After waiting 15 seconds, the experimenter continued.] If you have not heard the voice or voices yet, you should be hearing them at any moment. [After a lapse of 30 additional seconds, the experimenter gave instructions for the three maneuvers.] [Mouth] Now I want each of you to open his or her mouth as widely as is comfortable while remaining relaxed. [Ears] Now I want each of you to put the forefinger of your right hand into your right ear, and the forefinger of your left hand into your left ear, as deep as is comfortable. [Eyes] Now I want each of you to squeeze your eyes as tightly shut as is comfortable for you.

Each maneuver was maintained for a period of 30 seconds. Pauses of 15 seconds intervened between maneuvers, which were administered in a counterbalanced order. The number of subjects in each order varied from six to 17. All sessions were held on weekends to minimize the possibility that voices outside the experimental room might be mistaken for a hallucination.

After the three maneuvers had been completed, the experimenter announced that the voice or voices were gone and could no longer be heard. The group was brought out of the trance and immediately completed the Harvard scale. Each subject was then interviewed individually by the first author. If the subject reported that there had been no hallucination, he or she was paid $5 for participating and was dismissed. The subjects who had hallucinated were asked what effect, if any, each maneuver had had (not specified any further). If the subject reported that none of the maneuvers had blocked the hallucination, he or she was asked directly whether the voices had still been heard when all three maneuvers were completed. Subjects who hallucinated were carefully debriefed to preclude any possible residual effect. All subjects were asked what they thought the purpose of the experiment might be.

## RESULTS

Sixteen (25%) of our 64 subjects reported auditory hallucinations in response to the experimenter's suggestion. Table 1 lists the characteristics of the hallucinator and nonhallucinator subgroups. Overall, the majority of the subjects were female, were employed rather than students, were in their 30s, were moderately good hypnotic subjects as measured by the Harvard scale, and had had no previous experience with hypnosis. Nearly half of the subjects had a positive rating on the fly hallucination item of the Harvard scale, in which it is suggested to the subject that he or she hears a fly buzzing close by. There were no significant differences between the hallucinator and nonhallucinator subgroups on any of these six variables. No subject was able to identify accurately the purpose of the investigation.

The crucial data concern the success of the three maneuvers in abolishing the hypnotically induced

**TABLE 1. Characteristics of 64 Normal Subjects Who Did or Did Not Experience Auditory Hallucinations Induced by Hypnosis**

| | Age (years) | | Male Sex | | Student | | Harvard Scale[a] Score | | Previous Hypnosis | | Positive Rating on Fly Hallucination Item | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group | Mean | SD | N | % | N | % | Mean | SD | N | % | N | % |
| Hallucinators (N=16) | 33.9 | 9.17 | 6 | 37.5 | 5 | 31.3 | 6.75 | 3.80 | 5 | 31.3 | 7 | 43.8 |
| Nonhallucinators (N=48) | 34.8 | 4.03 | 16 | 33.3 | 15 | 31.3 | 5.60 | 1.69 | 12 | 25.0 | 21 | 43.8 |
| Total (N=64) | 34.6 | 5.69 | 22 | 34.4 | 20 | 31.3 | 5.89 | 3.66 | 17 | 26.6 | 28 | 43.8 |

[a]Harvard Group Scale of Hypnotic Susceptibility.

hallucinations. The maneuver of forefingers in the ears was reported to have ended hallucinations in four subjects, who performed the maneuvers in three different orders. No subject reported that a hallucination, once abolished, returned. No subject reported that either the mouth or the eye maneuver abolished a hallucination.

## DISCUSSION

Obviously, our results are totally different from those of Bick and Kinsbourne (1). Eighty-six percent of their hypnotized normal subjects behaved in a way that supported the subvocalization hypothesis. None of ours did. Not a single one of our subjects reported that his or her hallucination was abolished by the mouth maneuver, while four subjects reported success with fingers in the ears, a behavior that is more remote from subvocalization than opening the mouth.

There are a number of possible explanations for the discrepancies in the two reports. Fewer of our subjects were students and a higher proportion were women. However, it is difficult to surmise how these demographic differences could have materially affected the results. On the average, our subjects were certainly at least moderately susceptible to hypnosis. The 25% rate of hallucination was about as expected. Nearly half the subjects had positive scores on the fly hallucination item of the Harvard scale. However, a subject need not actually hear a buzzing sound to obtain a passing score on this item. It is conceivable that the group administration may have somehow affected the findings, but this seems unlikely. It was to preclude just such an eventuality that each subject was interviewed individually after the experiment proper was completed. No subject correctly identified the purpose of the investigation, so there is no reason to believe that demand characteristics affected the results.

The most likely explanations for our conflicting results lie in the design of the Bick and Kinsbourne study. Before participating, their subjects knew fairly well what might be required of them. It has been demonstrated (6) that hypnotized subjects are highly susceptible to demand characteristics of experiments in which they report whether they had hallucinations. The 60% success rate obtained by Bick and Kinsbourne seems very much like an effect of experimenter demand. It would also not be far-fetched to suggest that Bick and Kinsbourne in some manner conveyed to their subjects not only a demand to hallucinate but also a demand to abolish hallucinations by the mouth maneuver and not by the eye and fist maneuvers.

Our findings have no bearing on the segment of Bick and Kinsbourne's investigation that dealt with schizophrenic patients. Our results do, however, strongly suggest that the part of the investigation which involved normal hypnotized subjects was flawed and that the results cannot be used to support the subvocalization hypothesis.

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# Not All That Moves Is Tardive Dyskinesia

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*Objective: Because tardive dyskinesia and spontaneous dyskinesia appear the same, it is difficult to determine whether an individual patient's abnormal movements are induced by medication or have developed spontaneously. Therefore, estimates of the prevalence of tardive dyskinesia that are based on observations not adjusted for spontaneous dyskinesia are inflated. In addition, age is thought to be an important risk factor in the development of both tardive and spontaneous dyskinesias. The authors estimate the prevalence of both disorders for specific age groups. Method: The authors reviewed nine reports on dyskinesia prevalence that included history of neuroleptic treatment and related prevalence to age. A rating of 2 or more on the Abnormal Involuntary Movement Scale or an equivalent score on another scale was considered an indication of dyskinesia. If the subject had taken neuroleptics for more than 3 months, the movement disorder was classified as neuroleptic-associated dyskinesia; other dyskinesias were considered spontaneous. The prevalence of tardive dyskinesia was defined as the rate of neuroleptic-associated dyskinesia minus the rate of spontaneous dyskinesia. Results: The true rate of tardive dyskinesia was below 20% for all age groups except 70–79 years. The correlation between the rate of neuroleptic-associated dyskinesia and the rate of spontaneous dyskinesia was low. Conclusions: After age 40 the prevalence of spontaneous dyskinesia is sufficiently high to conclude that many patients with diagnoses of tardive dyskinesia have abnormal movements attributable to causes other than neuroleptics.*

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Tardive dyskinesia is a syndrome of abnormal involuntary movements that develops in some patients during long-term treatment with neuroleptics. It is characterized by choreoathetoid movements, usually in the orofacial area but sometimes in the limbs and trunk (1). Estimates of the prevalence of tardive dyskinesia vary from 0.5% to 65% (2). To estimate the true risk of developing tardive dyskinesia it is necessary to know the risk, to patients who have what appear to be neuroleptic-associated abnormal movements, of developing similar movements (spontaneous dyskinesia) if they had never taken neuroleptics.

Spontaneous dyskinesia consists of movements phenomenologically similar to neuroleptic-induced dyskinesia and was described by Kraepelin (3) in patients with schizophrenia long before the introduction of neuroleptics. A recent retrospective examination of Ticehurst House Asylum casebooks in England (4), covering the years 1850 to 1889, showed that over 25% of the patients with schizophrenia (diagnosed with the Research Diagnostic Criteria [5]) had movements which today would be described as tardive dyskinesia. The prevalence of spontaneous dyskinesia has been reported to be anywhere between 0% and 53% (6).

Because spontaneous dyskinesia and tardive dyskinesia appear phenomenologically the same, it is difficult or impossible to determine whether an individual patient's abnormal movements are induced by medication or have developed spontaneously. Therefore, estimates of the prevalence of tardive dyskinesia that are based on observations not adjusted for spontaneous dyskinesia will be inflated.

If there were a reliable estimate of tardive-dyskinesia-like movements from the preneuroleptic era, it would be possible to calculate the true risk of developing tardive dyskinesia by subtracting that rate from the current rate of patients who are being treated with neuroleptics and have movement disorders. Unfortunately, preneuroleptic surveys of abnormal movements in psychiatric populations are few in number, generally do not present percentages, and are further limited by the absence of specified criteria that can be used to make comparisons with neuroleptic-era studies.

Fortunately, however, since the introduction of neuroleptics, surveys have been performed on patients never treated with neuroleptics. From a list of 19 studies carried out between 1966 and 1984, Casey and

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**TABLE 1. Studies Showing Age-Related Prevalences of Neuroleptic-Associated and Spontaneous Dyskinesias**

| Study | N | Age (years, mean or range) | Description of Subjects | Percent With Dyskinesia | | Comments |
|---|---|---|---|---|---|---|
| | | | | Neuroleptic-Associated | Spontaneous | |
| Greenblatt et al., 1969 (9) | 153 | 72 | Nursing home patients and psychiatric patients | 38.5 | 2 | Over 34% of the patients had chronic brain syndromes |
| Crane and Smeets, 1974 (10) | 39 | 63–89 | Recently admitted geriatric patients in a state hospital | 51.6 | 25.0 | |
| Bourgeois et al., 1980 (11) | 270 | 76 | Elderly subjects in a retirement home | 42 | 18 | |
| Blowers et al., 1981 (12) | 500 | 82.7 | Residents of homes for the elderly | 48.4 | 31.7 | |
| Kane et al., 1982 (13) | 151 | 72.3 | Normal elderly | 13 | 8 | Higher ratings used as criteria to be consistent with studies that did not use global ratings |
| Barnes et al., 1983 (14) | 182 | 24–78 | Psychiatric patients | | | Prevalence of neuroleptic-associated dyskinesia for chronic schizophrenic patients not significantly different from prevalence for all psychiatric patients aged 60 or older |
| | | ≤39 | | 21 | | |
| | | 40–49 | | 24 | | |
| | | 50–59 | | 26 | | |
| | | ≥60 | | 49 | | |
| | 85 | 17–81 | Drug-free normal subjects | | | |
| | | ≤39 | | | 2 | |
| | | 40–49 | | | 11 | |
| | | 50–59 | | | 26 | |
| | | ≥60 | | | 14 | |
| | 43 | 60–89 | Chronic schizophrenic inpatients | 49 | | |
| Lieberman et al., 1984 (15) | 400 | 73.1 | Normal elderly | | 1.2 | Low rate of movement disorders in normal elderly due partly to stringent diagnostic criteria |
| | 291 | 83.3 | Untreated geriatric patients with organic brain syndrome | | 4.8 | |
| | 79 | 85.5 | Treated geriatric patients with organic brain syndrome | 16.5 | | |
| Chorfi and Moussaoui 1985 (17, 18) | 100 | 16–32 | Schizophrenic patients | 14 | 0 | |
| Chacko et al., 1985 (16) | 87 | 67 | Elderly psychiatric outpatients with mixed diagnoses | 47 | 26 | Disproportionately high number of women |

Hansen (6) calculated the prevalence of abnormal involuntary movements in treated and untreated institutionalized patients who had been evaluated by the same investigators using the same assessment techniques. Gerlach and Casey estimated that the prevalence of neuroleptic-associated dyskinesia was 19.8% and the rate of spontaneous dyskinesia was 5.9% (7). The difference, 13.9%, is the true prevalence of tardive dyskinesia. Similar results were obtained by Morgenstern et al. (8), who conducted a meta-analysis of data from 21 studies published between 1966 and 1985. They estimated that neuroleptic exposure accounted for 65% of tardive-dyskinesia-like movements in patients who had been exposed to neuroleptics for at least 3 months; 35% of the movements were from other causes. Neither study specifically calculated the effect of patient age on the prevalence of tardive or spontaneous dyskinesia.

Since age is thought to be an important risk factor in the development of both tardive and spontaneous dyskinesias, we estimated prevalence across various age groups for both disorders. On the basis of these estimates we calculated the age-related risk of developing true tardive dyskinesia for patients who must take long-term neuroleptics.

## METHOD

To the relevant English-language studies covered by Casey and Hansen (9–15) and one other English-language study (16), we added one study published in French (17). The French study (17, 18) is important because it adds to the representation of the 16–32-year age group. To differentiate between spontaneous and tardive dyskinesia, only studies that clearly indicated the presence or absence of neuroleptic histories were included. Similarly, only studies in which prevalence was matched with age were used. Table 1 describes the studies that fit these criteria.

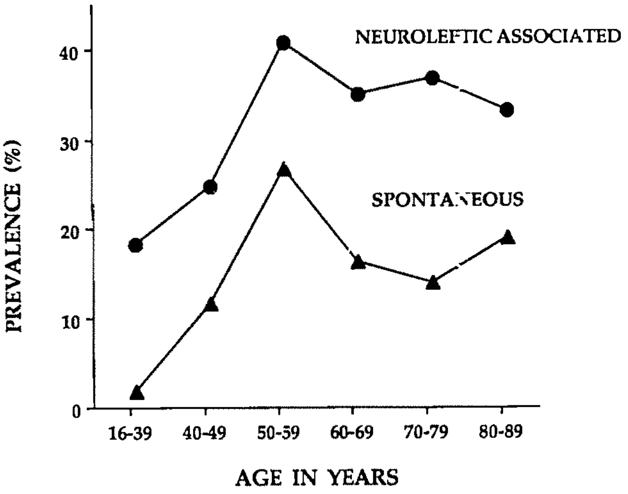
Abnormal movement rating scales and diagnostic methods varied among the studies; approximately one-half used the Abnormal Involuntary Movement Scale (AIMS) (19) or the Simpson scale or modified Simpson scale (20), and the rest employed less widely used methods and instruments (table 2). Generally, the studies included both males and females aged 16 to 89 years. We were able to divide the subjects by decades of life—40–49, 50–59, 60–69, 70–79, and 80–89 years old—with the exception of the 16–39-year-old group. Unweighted or arithmetic means were calculated for each age group to determine the general risk of developing a dyskinetic movement.

**TABLE 2. Rating Instruments and Diagnostic Methods Used in Studies of Neuroleptic-Associated and Spontaneous Dyskinesias**

| Study | Rating Instrument | Diagnostic Criteria |
|---|---|---|
| Greenblatt et al., 1969 (9) | Rating scale developed by Crane | Presence or absence of dyskinesia rated first by experienced registered nurse and college student independently, then blindly by experienced psychiatrist |
| Crane and Smeets, 1974 (10) | 7-point rating scale | Rating based exclusively on observed motor abnormalities in oral region; severity was measured from 0 (absent) to 6 (extreme), although last two ratings were not used |
| Bourgeois et al., 1980 (11) | Villeneuve Rating System | Orofaciallingual movements and movements of extremities were rated |
| Blowers et al., 1981 (12) | Modification of AIMS | No scores provided, but movements described as mostly mild |
| Kane et al., 1982 (13) | Modified Simpson Dyskinesia Scale | Raters trained in assessment of abnormal involuntary movements, used standardized examination format |
| Barnes et al., 1983 (14) | Barnes and Trauer tardive dyskinesia rating technique | Patients videotaped while taking simple reading test; ratings were blind and based on duration of movement over time |
| Lieberman et al., 1984 (15) | Simpson dyskinesia scale, AIMS, and modified 11-item Scale for EPS | Global ratings of at least mild tardive dyskinesia by two independent examiners required to designate positive case |
| Chorfi and Moussaoui, 1985 (17, 18) | AIMS | Details not provided |
| Chacko et al., 1985 (16) | AIMS | Tardive dyskinesia considered present if AIMS score was 2 (mild) or above on any of the seven items |

An abnormal movement rating of 2 or more on the AIMS (a rating of 1 on the AIMS denotes a minimal movement, which is defined as the extreme of normal) or its equivalent on another rating scale was considered a positive indication of neuroleptic-associated dyskinesia if the subject had a neuroleptic history of more than 3 months. A period of 3 months was selected as a threshold because it is generally accepted that tardive dyskinesia rarely occurs before 3 months of neuroleptic treatment, although a few such cases have been reported (21–23). If the authors provided reasonable assurance that the patient did not have a history of neuroleptic exposure of more than 3 months and the patient had a rating of 2 or higher, these abnormal movements were attributed to spontaneous dyskinesia. Although we did not attempt to evaluate the primary psychiatric diagnoses of the patients, the studies tended to include similar patients in the treated and untreated groups.

**FIGURE 1. Mean Prevalence by Age of Neuroleptic-Associated Dyskinesia and Spontaneous Dyskinesia in Subjects Who Had Taken Neuroleptics for Longer Than 3 Months**[a]

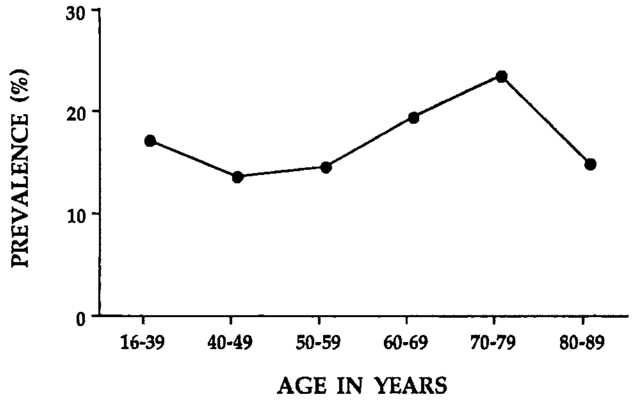


[a] Based on nine studies (9–18). The number of studies (N) for each age group is as follows: 16–39, N=2; 40–49, N=1; 50–59, N=1; 60–69, N=2; 70–79, N=4; 80–89, N=2. The number of patients for each age group is 16–39: N=45 and N=2 for neuroleptic-associated and spontaneous dyskinesia, respectively; 40–49: N=43 and N=9; 50–59: N=72 and N=22; 60–69: N=119 and N=18; 70–79: N=63 and N=53; 80–89: N=72 and N=134.

## RESULTS

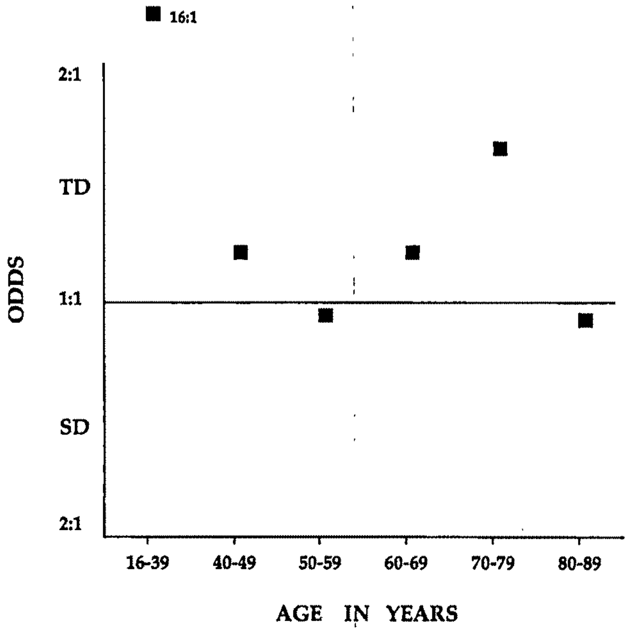
The mean prevalence by age of neuroleptic-associated dyskinesia and spontaneous dyskinesia is presented in figure 1. Both neuroleptic-associated and spontaneous dyskinesia increase with age, although neuroleptic-associated dyskinesia appears to reach its zenith in the sixth decade of life, when the rate for spontaneous dyskinesia is comparatively low (figure 1). Figure 2 shows the true prevalence of tardive dyskinesia, i.e., the prevalence of spontaneous dyskinesia subtracted from total dyskinesias in the neuroleptic-treated patients. The true tardive dyskinesia prevalence is below 20% for all age groups except 70–79 years; it appears to rise in the seventh and eighth decades and return to a fairly stable baseline in the ninth decade. It is interesting that the correlation between neuroleptic-associated and spontaneous dyskinesia was low (Spearman's rho=0.25). The Friedman Block/Treatment test (a nonparametric two-way analysis of variance), which was used to compare neuroleptic-associated and spontaneous dyskinesia across age groups, indicated a nonsignificant difference ($t=0.66$, $df=11$, $p<0.41$). The higher prevalence of neuroleptic-associated dyskinesia in the 70–79 age group approached but did not achieve statistical significance (Wilcoxon signed rank test, $p<0.2$). While the authors of other reviews (1, 2, 24) have noted a direct correlation between the year of publication of a study and the prevalence of tardive

FIGURE 2. True Mean Prevalence of Tardive Dyskinesia by Age in Subjects Who Had Taken Neuroleptics for Longer Than 3 Months[a]



[a]Based on nine studies (9–18). Prevalence of tardive dyskinesia was calculated as the prevalence of neuroleptic-associated dyskinesia minus the prevalence of spontaneous dyskinesia.

FIGURE 3. Relative Risk of Tardive Dyskinesia, Compared With Spontaneous Dyskinesia, in Subjects of Different Ages Who Had Taken Neuroleptics for Longer Than 3 Months and Had Tardive-Dyskinesia-Like Movement Disorders[a]



[a]Based on nine studies (9–18). The relative risk is the ratio of the risks for the two disorders.

dyskinesia, there was no significant correlation between the year of a study's publication and the prevalence of neuroleptic-associated dyskinesia (rho=0.12) or spontaneous dyskinesia (rho=0.43) for the studies we reviewed. The somewhat stronger correlation for spontaneous dyskinesia than for neuroleptic-associated dyskinesia is consistent with the findings of Morgenstern at al. (8). When the prevalence of spontaneous dyskinesia was subtracted from the prevalence of neuroleptic-associated dyskinesia to determine the prevalence of tardive dyskinesia and those numbers were correlated with the year of publication, there was a nearly significant inverse relationship (rho=–0.63, $p<0.1$, two-tailed). Because none of the correlations was statistically significant and the number of studies was small, no attempt to covary for the year of publication and age-related prevalence was made.

Figure 3 shows the age-related odds of directly attributing abnormal movements to neuroleptic treatment in a patient who exhibits abnormal involuntary movements and has taken neuroleptics for longer than 3 months.

## DISCUSSION

By definition, tardive dyskinesia occurs only after long-term exposure to neuroleptics. Nevertheless, a question that has been asked many times is raised here once more: Does neuroleptic treatment play an etiologic role in hyperkinetic dyskinesias? Owens et al. (25) compared chronic schizophrenic inpatients treated with neuroleptics to a similar group never treated with neuroleptics, and the findings are of considerable importance. It is the only study of its kind because both groups of patients had similar disorders with similar severity and they were assessed at the same time by means of standardized techniques. Surprisingly, there were few significant differences between the groups in prevalence, severity, or distribution of abnormal movements. At face value this study indicates that neuroleptics are not responsible for dyskinetic movements, and, in fact, the authors stated, "The exact relationship between involuntary movement disorders and neuroleptic medication in chronic schizophrenia remains to be determined" (25, p. 461).

The prevalence of tardive dyskinesia, however, increases with age, and the patients in the Owens et al. study who were never treated with neuroleptics were 9.5 years (mean) older than the neuroleptic-treated patients. In a subsequent analysis, in which the patients were matched for age, the prevalence of dyskinesia in the neuroleptic-treated group was significantly higher ($p<0.05$) than in the never-treated group (6, 26). The age-adjusted reanalyses of this study and most other studies strongly indicate that neuroleptics are responsible for some but not all abnormal involuntary movements in patients taking neuroleptics.

As highlighted by the Owens et al. study, it is important for understanding tardive dyskinesia's epidemiology and pathophysiology, as well as for clinical applications, to know the risk of its development. Since increased age appears to be an important risk factor for developing tardive dyskinesia, we have attempted to provide estimated risks for specific ages.

A major obstacle in estimating the age-related risk of tardive dyskinesia is the paucity of studies providing age-related prevalence rates for neuroleptic-associated dyskinesia, spontaneous dyskinesia, or both. The number of studies is increased if both studies of paired subjects (age-specific prevalences of neuroleptic-associated dyskinesia and spontaneous dyskinesia in age-matched subjects) and studies of unpaired subjects (age-specific prevalences of neuroleptic-associated dyskinesia alone and spontaneous dyskinesia alone) are combined. In studies of unpaired subjects, however, the variance increases dramatically because these studies 1) tend to use dissimilar patient groups and 2) do not systematically examine neuroleptic-associated and spontaneous dyskinesia with identical measures. Therefore, we used only studies of neuroleptic-associated dyskinesia and spontaneous dyskinesia in patients examined by the same investigators.

After we divided the subjects by decade of life (i.e., 16–39, 40–49, 50–59, 60–69, 70–79, and 80–89), it became apparent that the data were sparse. Because the patients were inconsistently matched for gender we were unable to separate male and female subjects, but, among the studies reporting gender as well as age, the risk for females was higher than for males. Unfortunately, even though we chose to include only studies that examined patients both with and without neuroleptic exposure by means of the same assessment techniques, there is little assurance that in most of the studies patients in the same decade of life were matched either by primary diagnosis or severity of illness.

Casey and Hansen (6) used weighted means, a method that gives greater consideration to studies with more subjects and hence may be more representative of the population of interest. Unfortunately, use of weighted means can easily exaggerate the value of a poorly or idiosyncratically performed study that happens to include a greater number of patients. Since studies conducted in the late 1960s, in particular, had larger numbers of subjects and did not use standardized methods of assessment, we felt that using unweighted means would provide more valid estimates.

Another limitation of our study is that neuroleptics substantially mask dyskinetic movements. Masking of tardive dyskinesia by neuroleptics would be expected to lower the perceived prevalence of tardive dyskinesia. On the other hand, neuroleptic dose reductions (leading to withdrawal dyskinesias in some cases) and the administration of anticholinergic medications in the neuroleptic-treated patients would be expected to produce inflated tardive dyskinesia prevalences. We were unable to determine the relative weight these factors should be given in our calculations, but undoubtedly they have influenced our estimates somewhat.

It is striking that the true prevalence of tardive dyskinesia changes relatively little with increasing age. The slight increase in prevalence of tardive dyskinesia after the sixth decade could be caused by many factors, some of which are worthy of a brief discussion. It is very possible that the increased prevalence with increasing age is the result of a measurement error. This would seem to be especially likely given the small number of studies contributing to each age group.

One would expect there to be an accumulation of cases from one decade to another. It is surprising that there is not a steady rise in cases with increasing age. At any rate, the apparent increased prevalence after the sixth decade could be due to accumulation of patients who had developed tardive dyskinesia in early decades of life. Because of our method of calculation of tardive dyskinesia prevalence (subtraction of the rate of spontaneous dyskinesia from the rate of neuroleptic-associated dyskinesia), this would be highlighted by the decreased prevalence of spontaneous dyskinesia that seems to occur in the seventh decade.

Another possible explanation is that patients' likelihood of developing abnormal involuntary movements during neuroleptic treatment may increase with increasing age (27). Finally, it is possible that the movements of tardive dyskinesia are physiologically the same as spontaneous movements but that neuroleptics make them appear earlier than they would otherwise if the patients never took neuroleptics (28). Since the risk of developing tardive dyskinesia appears to increase with the length of time a patient takes neuroleptics, the age-related prevalence of tardive dyskinesia suggests that the cumulative risk plateaus after a period of time. Robinson and McCreadie (29) surveyed the point prevalence of tardive dyskinesia in schizophrenic patients from a discrete geographical area and reported it to be 31% in 1981, 27% in 1982, and 30% in 1984. The authors suggested that the prevalence of tardive dyskinesia in a community of schizophrenic patients had reached a plateau. Barnes et al. (30), however, in a 3-year follow-up study of patients examined for tardive dyskinesia, reported an increase in the point prevalence of dyskinesia from 39% to 47%. In an ongoing prospective study, Kane et al. (27) found a curvilinear relationship between age and tardive dyskinesia: the risk remained fairly stable between ages 20 and 40 and rose with increases in age. In a 5-year prospective longitudinal study of a cohort of schizophrenic outpatients, Chouinard et al. (31) did not find the effect of age to be significant but reported a twofold increase in prevalence, concluding that vulnerability to severe parkinsonism, poor schizophrenia prognosis, and long duration of neuroleptic treatment (5 years) were important risk factors for the development of tardive dyskinesia. It is interesting that the mean ages of the patients studied by these investigators varied (32): Kane et al. (27), 28 years; Chouinard et al. (31), 42 years; and Barnes et al. (30), 56 years.

Finally, the slight decrease in the prevalence of both neuroleptic-associated and spontaneous dyskinesias during the seventh decade (figures 1 and 2) might be related to a number of factors, including remission of the disorder and—in the case of neuroleptic-associated dyskinesia—suppression of movements by higher neuroleptic doses (masking), altered neuroleptic metabolism, and death. Explanation of these findings will clearly require further exploration.

We were impressed that in the studies which met our criteria the rate of tardive dyskinesia appeared to decrease with time and the rate of spontaneous dyskinesia increased. An analysis of covariance, however, did not reveal a significant difference between the slopes of these two lines.

The data presented should be relevant to the clinician, who must weigh the risk of a patient developing tardive dyskinesia and what the patient is told. The prevalence of spontaneous dyskinesia after the age of 40 is sufficiently high to warrant the conclusion that many patients who might be diagnosed as having tardive dyskinesia because of the presence of neuroleptic treatment could have movement disorders properly attributed to causes other than neuroleptics. The ratio of tardive dyskinesia to spontaneous dyskinesia (figure 3) suggests that, with the exception of individuals in the 16–39 and 70–79 age groups, making a diagnosis of tardive dyskinesia in any given patient is difficult.

Although age remains the most consistent patient-related risk factor associated with the development of tardive dyskinesia (32), further work is needed to define more clearly other contributing factors. We have estimated the general risk of developing an abnormal dyskinetic movement across specific age groups. This information has important implications for patients who are interested in the long-term use of antipsychotic medications. Since many patients will develop abnormal movements regardless of whether they take neuroleptics, our data suggest that the risks from these medications are somewhat less than is generally thought.

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# Imipramine Treatment of Methadone Maintenance Patients With Affective Disorder and Illicit Drug Use

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Ronald Brady, M.D., and Jonathan W. Stewart, M.D.**

*Of 17 consecutive patients receiving methadone maintenance treatment who had primary or chronic depression, nine (53%) improved in both mood and drug abuse after imipramine treatment. This finding suggests a potential for helping such dual-diagnosis patients reduce drug abuse and associated risk for HIV. Further controlled trials are warranted.*

(Am J Psychiatry 1991; 148:667–669)

Methadone maintenance is frequently complicated by continued drug abuse and associated behaviors that place the patient at high risk for HIV. A fraction of these patients may have affective disorder and use illicit drugs to "self-medicate." In such patients antidepressant treatment might improve both mood and drug abuse.

Six studies have tested the use of tricyclic antidepressants to treat depressed methadone patients (1–5 and unpublished study by B. Goldstein and associates described by Woody et al. [6]). Most showed improvement in depressive symptoms (3–5 and Goldstein et al.), but there was little evidence for reduction in drug abuse. The limitations of these studies include small sample sizes, short trial lengths, and modest tricyclic doses. Perhaps most important, in all studies depression was diagnosed on the basis of cross-sectional symptoms. Longitudinal studies have shown that most depression in opiate addicts is transient (7–9), perhaps representing drug-induced or situational dysphoria rather than medication-responsive affective disorder. Supporting this idea are the high rates of response to placebo in several trials (1, 2, and Goldstein et al.). We therefore carried out an open pilot trial of imipramine for methadone patients with primary or chronic depression identified with criteria based on lifetime history.

## METHOD

The subjects were 17 patients (table 1) currently in methadone maintenance treatment at a community-based clinic who also met the *DSM-III-R* criteria for major depression (N=10) or dysthymia (N=7) that 1) was primary (antedated substance abuse on a lifetime basis) (N=9), 2) had occurred during at least 3 months of abstinence in the past (N=5), or 3) had lasted at least 6 months during the current episode (N=3).

The median duration of the current depressive episode was 10 years (range: 8 months to 32 years). Seven patients also had panic disorder. Diagnosis was made on the basis of clinical history by experienced research psychiatrists (E.V.N., F.M.Q.). The patients were a consecutive series; some were recruited by random screening, but most were referred by their counselors because of depression and persistent drug abuse.

The patients were seven men and 10 women; 14 were non-Hispanic white, two were Hispanic, and one was black. Seven of the patients were unemployed. A

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**TABLE 1. Outcome of Imipramine Trial for Depressed Methadone Maintenance Patients**

| | | | | | Imipramine Treatment | | Hamilton Depression Score | | Percent of Urine Tests Positive for Illicit Drugs | |
|---|---|---|---|---|---|---|---|---|---|---|
| Patient | Age (years) | Sex | Diagnosis | Drugs Abused[a] | Dose (mg/day) | Duration | Baseline | Week 12 | Baseline | Weeks 6–12 |
| Responders | | | | | | | | | | |
| 1 | 22 | F | Major depression | Intravenous heroin | 300 | 9 months | 16 | 1 | 71 | 14 |
| 2 | 35 | M | Dysthymia | Diazepam, intravenous heroin | 125 | 9 months | 15 | 3 | 10 | 7 |
| 3 | 32 | M | Major depression | Free-base and intravenous cocaine | 300 | 8 months | 19 | 3[b] | 43 | 0 |
| 4 | 39 | M | Dysthmia | Free-base and intranasal cocaine | 200 | 5 months | 11 | 2 | 65 | 50 |
| 5 | 44 | F | Major depression | Heroin craving[c] | 300 | 11 months | 26 | 1 | 0 | 0[c] |
| 6 | 40 | M | Dysthymia | Heroin, diazepam | 300 | 10 months | 12 | 2 | 60 | 19[d] |
| 7 | 30 | F | Major depression | Intravenous cocaine, heroin | 250 | 9 months | 17 | 3 | 56 | 8 |
| 8 | 35 | M | Dysthymia | Intravenous cocaine, heroin | 250 | 9 months | 18 | 0 | 73 | 37 |
| 9 | 35 | F | Major depression | Intravenous cocaine, heroin | 200 | 10 months | 19 | 1 | 24 | 3 |
| Nonresponders | | | | | | | | | | |
| 10 | 30 | F | Dysthymia | Intravenous heroin | 100 | 6 months | 14 | 5 | 100 | 100 |
| 11 | 38 | F | Dysthymia | Intranasal cocaine, heroin | 250 | 6 weeks | 14 | 13[b] | 61 | 100[e] |
| 12 | 34 | F | Dysthymia | Free-base cocaine | 300 | 4 months | 14 | 2 | 55 | 25[f] |
| 13 | 26 | F | Major depression | Intravenous heroin | 150 | 5 months | 16 | 12 | 60 | 62 |
| 14 | 37 | M | Major depression | Diazepam | 250 | 8 weeks | 22 | 6[b] | 52 | 100[e] |
| 15 | 39 | M | Major depression | Intranasal cocaine, heroin | 250 | 4 months | 20 | 10[b] | 63 | 43 |
| 16 | 31 | F | Major depression | Intravenous heroin | 100 | 6 weeks | 19 | 3[b] | 38 | 20[e] |
| 17 | 29 | F | Major depression | Free-base cocaine | 300 | 5 months | 23 | 8 | 90 | 33 |

[a] "Free-base" includes free-base and crack cocaine.
[b] Hamilton score at week 6.
[c] Craving only (no use) at baseline, very much reduced after treatment.
[d] Continued use of prescribed diazepam but stopped on request.
[e] Across 4 weeks before end of study for patients who completed less than 12 weeks.
[f] Continued heavy alcohol abuse.

history of affective or panic disorder in first-degree relatives was probable for six patients and possible for five others. All but one were currently using illicit drugs, and nine used drugs intravenously. One (patient 5) was abstinent but had strong drug cravings and was included because we felt she was at high risk of drug relapse if untreated.

An additional seven patients, four women and three men, dropped out within 3 weeks of beginning imipramine treatment because of noncompliance (N=5) or side effects (N=2). These patients otherwise resembled the 17 completers demographically and diagnostically.

After giving informed consent, the patients began taking imipramine "open label." The dose was increased weekly in 50-mg increments as tolerated, and the maximum dose ranged from 100 to 300 mg/day (median: 250 mg/day). The trial length ranged from 6 weeks to 11 months. The Hamilton Rating Scale for Depression was administered at baseline and at weeks 6 and 12. Self-reported drug use was recorded weekly. Weekly complete urine drug screens were available for up to 6 months before and throughout imipramine treatment. The proportion of positive urine tests during treatment was computed with all values after week 6 in order to reflect the entire follow-up period.

## RESULTS

All but two patients (patients 11 and 13) experienced a marked reduction in depression and panic symptoms during imipramine treatment. As shown in table 1, nine patients (53%) were classified as responders. They either became completely abstinent (patients 3, 5, and 7) or achieved at least 1 month of abstinence with intermittent lapses. Lapses occurred upon exposure to persons or situations associated with past drug use (patients 1, 4, and 9) or during severe stress, such as divorce (patient 8) or the death of a loved one (patients 2 and 6). One of these patients (patient 8) continued drug abuse and dropped out. The rest were able to resume abstinence. Eight patients (47%) were considered nonresponders because they were unable to mount stretches of abstinence, although two (patients

12 and 17) achieved a partial benefit and reduced the frequency of their drug abuse.

## DISCUSSION

Our findings depart from the existing literature in suggesting that tricyclic antidepressants may help reduce illicit drug use in depressed methadone maintenance patients. Our results may arise from higher medication doses and a longer trial length. However, we suspect our use of lifetime criteria to determine primary or chronic affective disorder (rather than cross-sectional symptoms) to be the most critical factor.

The study has serious limitations. Because it is an uncontrolled, open-label trial, the rate of response to placebo could be high as in several prior studies (1, 2, and Goldstein et al.). We saw our patients weekly and, in addition to medication adjustment, provided support and relapse prevention strategies. This added professional attention could have engendered a placebo effect. On the other hand, our patients had chronic symptoms despite longstanding methadone treatment and related counseling and would thus seem unlikely placebo responders.

A potential drawback is that our subjects were heterogeneous. We included patients with dysthymia in addition to those with major depression because in our experience they respond to medication (10) and because we were seeking patients with chronic dysphoria, who we find have low rates of response to placebo (10). The high rate of comorbid panic disorder (seven of 17) is common in depressed patients. Panic disorder also responds to imipramine. At the same site we treated a patient with panic disorder alone, and he subsequently reduced his diazepam abuse substantially. Finally, our patients were abusing a variety of drugs and combinations. This is characteristic of methadone patients. Also, the self-medication hypothesis holds that treatment of dysphoria should reduce drug abuse regardless of the specific drugs of choice.

The improvement in affective symptoms was more robust than the improvement in drug abuse. Many of the "nonresponders" had improved mood yet continued their drug abuse. Among the "responders," who achieved periods of abstinence, lapses occurred. This suggests the course of drug abuse is independent of the course of affective disease to some degree, limiting the impact of antidepressant treatment and highlighting the need for concurrent psychosocial intervention.

A final caveat is that the prevalence of primary or persistent affective disorder, as we have defined it, is probably low among methadone maintenance patients. In a random sample of women from the same methadone clinic, 16 (33%) of 48 met our criteria. Nine of these 16 were abusing drugs, intravenously in eight cases. This is consistent with the finding by Rounsaville et al. (8) that 21%–26% of opiate addicts have chronic dysphoria. If antidepressant medication helped one-half of such dual-diagnosis patients control drug abuse, it would be a useful treatment with implications for both the drug abuse and HIV epidemics. Further controlled trials are warranted.

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# Book Forum

## Nancy C. Andreasen, M.D., Ph.D., Editor

TEXTBOOKS

**Introductory Textbook of Psychiatry,** *by Nancy C. Andreasen, M.D., Ph.D., and Donald W. Black, M.D. Washington, D.C., American Psychiatric Press, 1991, 539 pp., $49.95; $35.00 (paper).*

Psychiatry in the United States has changed. It has become extremely interested in objective and reliable diagnoses; it has more specific treatments than it ever had before; and it is beginning to understand the biological components of the multi-etiologic processes that lead to the development of psychiatric problems. Although most departments of psychiatry convey to their medical students the excitement of the field, they have not had a textbook of psychiatry to complement these efforts. The *Introductory Textbook of Psychiatry* by Drs. Andreasen and Black represents not only the knowledge base but the spirit and excitement of the "new" psychiatry. It is the best textbook of psychiatry for medical students that I have seen to date. Most publishers and departments of psychiatry have lamented the lack of a good textbook, but this is no longer the case.

The book is divided into four sections. The first, Background, includes such topics as the history of psychiatry, diagnosis and classification, interviewing and assessment, laboratory tests, and the neurobiology of mental illness. Section two, Psychiatric Disorders, covers psychopathology, keeping fairly close to the *DSM-III-R* diagnostic categories. Section three, Special Topics, is devoted to suicide, AIDS, and disorders of childhood and adolescence. Section four, Treatment, deals with psychosocial and somatic treatments.

The text is exactly at the correct level for medical students in that it is neither overly detailed nor underplayed. It gives a clear descriptive picture of each disease entity as well as practical guidelines for diagnosis and treatment. The references are excellent and limited. (The limiting of references is useful because the student is not overwhelmed.) The tables are uniformly helpful, and the text has bold headings to highlight important points. Best of all, it is a very well-written and clear text, meant to teach and, particularly, to teach medical students. It is of interest to compare the chapter on neurobiology of mental illness (chapter five) in this text with the chapter written by Coyle in *The American Psychiatric Press Textbook of Psychiatry,* edited by Talbott, Hales, and Yudofsky (1), to see how simple this complex material has been made for medical students. The chapter by Drs. Andreasen and Black gives enough to whet students' appetite but not enough to mystify them.

The chapter on history puts psychiatry into a very clear framework for the medical student. In a similar vein, the chapter on diagnosis is not only a good overview of the rationale behind *DSM-III-R* but also an excellent discussion on how this nomenclature came into existence. The chapter on interviewing contains detailed descriptions of major psychiatric symptoms and how to elicit them, which should prove extremely useful to students. It also covers various structured interviews. All the phenomenological chapters are clear and comprehensive and have detailed tables and descriptive materials supported by data from the literature. It is a pleasure to see data so clearly interspersed to document phenomenology.

In sum, this is a superb textbook. It is authoritative and not overwhelming. It will be widely used and make most educators of medical students envious that they could not produce such a readable volume. I think it is a book that the field has been waiting for and is a credit both to the authors and to contemporary psychiatry. Drs. Andreasen and Black have made a significant contribution to the teaching of psychiatry and should be strongly commended by our field for doing so.

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**Clinical Psychiatry for Medical Students,** *edited by Alan Stoudemire, M.D. Philadelphia, J.B. Lippincott Co., 1990, 662 pp., $32.50 (paper).*

Although said to be written for medical students, this text would be useful to the psychiatry resident or even to the practitioner preparing for Board examinations. It is a well-organized volume that is practical in style and outline-oriented so that the reader will be able to find answers to questions. Each of the chapters has a series of charts or tables that summarize the high points. The number of tables per chapter depends on the content. Paragraph headings are introduced by boldface type. The readable typeface and attractive format show a thoughtful approach to production. This type of organization will appeal to the student who wants a rapid review of the facts about a clinical condition. Most of the chapters also have a summary at the end called Clinical Pearls, and these pearls also make the content easy to review. The standard format for the chapters on clinical conditions begins with a definition, then reviews epidemiology, diagnosis, differential diagnosis, etiology, and pathogenesis, and ends with an overview of clinical management. The orientation of the content is eclectic, including biological and psychodynamic points of view.

Each chapter has a general reading list applicable to its contents and accompanied by a more extensive series of references for the reader who wants to master some field in depth.

Any book with 47 contributors would be expected to show considerable unevenness, but Dr. Stoudemire has taken his job seriously. The format is even across chapters. The tables as well as the clinical pearls sections demonstrate consistency. Even the writing itself has a reasonable level of uniformity.

The book includes two chapters on assessment, ten on clinical disorders, five on symptoms, three on therapies, and two on special settings (emergency rooms and general medical practice). There is a chapter on child and adolescent psychiatry but none on geriatrics. One appendix offers a section on the problem-oriented approach to teaching and another provides an audiovisual guide listing videotapes to accompany and illustrate specific chapters. The first chapter, "Psychiatric Assessment, *DSM-III-R,* and Differential Diagnosis," has a useful appendix outlining *DSM-III-R*.

Deficiencies include the lack of separate chapters for geriatric psychiatry and for information about the function of the psychiatrist in certain specialized settings. For example, there is no adequate section about psychiatry in nursing homes, public hospitals, or community mental health centers, although psychiatrists spend considerable effort in such locations.

Dr. Stoudemire is to be congratulated for this practical and readable text. It will be easy for the experienced clinician to locate information for a rapid and competent review. Medical students will appreciate the organization that makes it possible to identify highlights and to prepare for the expected examinations. It is recommended for such audiences and purposes, but not as a reference work.

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## SUBSTANCE ABUSE

**Children of Alcoholics: Critical Perspectives,** *edited by Michael Windle and John S. Searles. New York, Guilford Press, 1990, 244 pp., $30.00.*

Beginning in the early 1980s a remarkable new concern arose on the medical-social horizon, centered on a sizable group of people called children of alcoholics. There were an estimated 28 million children of alcoholics in the United States—one out of every eight Americans. Conferences sprang up, well attended by social workers, alcoholism counselors, children of alcoholics, and a smattering of psychologists and psychiatrists. National foundations for children of alcoholics were established. A new lecture circuit came into existence starring experts on children of alcoholics, who often were themselves children of alcoholics.

The children of alcoholics movement was mainly promoted by people who adopted an environmentalist's explanation for alcoholism. Behind the movement is the assumption that children are mainly products of their upbringing. In a sense, the children of alcoholics movement has been a counterweight to genetic studies—keeping the nature-nurture controversy in a dynamic equilibrium.

Are children of alcoholics a special group of individuals who are prone to specific disorders requiring specialized care? The editors of this timely and well-organized book have performed a useful service for workers in the field by assembling a panel of 10 experts (eight plus the editors) who review the scientific literature bearing on this important question. They have reviewed more than 1,000 publications and are generous with theories to serve as foundations for future research. Most of the papers, it appears, are of "heuristic" value, meaning that the data are inconclusive. The editors acknowledge this: "It is important to recognize that the COA [children of alcoholics] research literature is in its infancy as a body of knowledge, that many contradictory findings have been reported . . . and that little evidence exists to suggest the kinds of preventions and interventions that are most likely to be helpful for COAs" (p. 217).

The chapters include reviews of the prevalence of alcoholism among children of alcoholics, biological markers, neuropsychological characteristics, genetics, temperament, family factors, and prevention/treatment approaches. Each chapter acknowledges the limitations of existing data; each ends with suggestions for future research.

Dominating the book is something called "new wave interactionism." In the preface, Robert Zucker quotes H.L. Mencken: "For every complex problem there is an easy answer . . . and it is wrong." New wave interactionism would suggest that for every complex problem there is a complex answer—and whether it is right or wrong is anybody's guess.

Fortunately, the value of the book does not depend on the adoption of any theoretical scaffold. The book should appeal to specialists from several disciplines who have not succumbed to dogma and rhetoric: researchers, educators, and clinicians.

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**Marijuana,** *by Mark S. Gold. New York, Plenum, 1989, 259 pp., $32.50.*

Along with alcohol and opium, marijuana ranks as one of the world's oldest intoxicants. In 1735 the Swedish botanist Carolus Linnaeus classified marijuana as *Cannabis sativa* and eased open a door for scientific research regarding an herb whose incorporeal properties have been appreciated in Eurasia for more than 4,000 years. Scientific thought regarding marijuana has often been at odds with social opinion, resulting in arguments simply because scientific evidence has been inconclusive, contradictory, or lacking. Even during the last decade of the twentieth century the risks and consequences of marijuana use are vehemently debated. Still, it remains a substance with entangling medical, social, and economic ramifications.

This book's premise is simple and straightforward: The answer to the question, Does marijuana cause health problems? is, from the viewpoint of a thoughtful physician and scientist, an unequivocal yes. Citing a wide array of current scientific evidence, Gold delineates the many ways that marijuana injures mind and body. He cites indisputable respiratory, immunologic, and endocrine impairments linked to marijuana use, and, despite the once-popular belief that "grass" lines the yellow brick road to true understanding, Gold thoroughly explores the telling psychiatric implications of cannabis abuse.

In the current clinical setting, marijuana abuse is often a landmark in the profile of individuals who practice polysubstance abuse. This complication, and the widespread view that marijuana use is harmless and "risk-free" (which presupposes, of course, that abusive behavior does not have inherent risks), can cloud the clinical picture. With this in mind, a book that offers an updated medical and psychological understanding of marijuana should be helpful to virtually all primary care specialists.

As with Gold's earlier writings on substance abuse (1–3), *Marijuana* is informative and comprehensive yet escapes being a weighty or laborious text. Graphs and tables are effectively used, and the style is streamlined, readable, and sprinkled with useful clinical illustrations. I was particularly impressed by the accessible organization. Each chapter couples evenly with the preceding but is capable also of standing alone, independently embracing its subject. Busy clinicians can readily tailor specific readings that are most suitable for their needs. A sampling of topics include the following: cannabinoid pharmacology, laboratory detection, medical problems, psychiatric problems, diagnosis, treatment, and some interesting views on prevention of cannabis abuse. All chapters are extensively referenced.

There are many reasons to recommend this book and few obvious criticisms. One may argue that the list price is a bit hefty for a small specialty text, but I know of no other work that so deftly handles the topic. It would be a valuable reference for general psychiatrists and other clinicians with a subspecialty interest in substance abuse.

As I considered an overall assessment of this book, an analogy occurred to me. I suspect that a few semesters have passed since many readers of this review have browsed the aisles of a collegiate bookstore gathering texts for undergraduate study. As I recall, next to each stack of books marked "required reading" was an assortment of texts marked "recommended reading." For the diligent student, the latter provided depth and background beyond rudimentary concepts. In my view, Mark Gold's work stands solidly in the domain of highly recommended reading.

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**Recent Developments in Alcoholism, vol. 7: Treatment Research,** *edited by Marc Galanter. New York, Plenum, 1989, 371 pp., $65.00.*

According to the editor, this volume deals with the issue of treatment research. In the foreword, Margaret Bean-Bagoy notes that "the overall value of this volume is to express and to facilitate a transformation going on in the field [of alcoholism]."

These two statements are important for the reader. This compendium of current research papers is divided into four sections. The first two are updates on clinical issues; one deals with data collected relative to Alcoholics Anonymous (AA), and the other deals with family dynamics in alcoholism. Sections three and four deal with biological issues; one presents the data on serotonin's ethanol preference, and the other focuses on the clinical pharmacology of serotonin, benzodiazepines, and lithium in alcoholic patients.

Each of these sections is important for physicians who consider themselves knowledgeable about alcoholism and alcoholic patients. Each section would also stand alone for the clinician or basic scientist who wishes to know the latest data about any of these areas.

When one reads the volume as a whole, the very disparate look of sections two and three can be a little disconcerting because the editor has let the editor of each section provide an introduction without any reference to the overall goals of the volume.

The first section is extremely important for any clinician in the field of alcoholism. AA and the 12-step model are the bastion for the majority of alcoholism treatment programming in the United States. At this point, there are a number of studies that challenge AA as a "stand alone" therapy. This section of the book not only deals with the results of those outcome studies but attempts to put AA in a historical perspective and as a backdrop for other therapeutic modalities. It also defines and outlines the concept of codependence according to *DSM-III-R*-style criteria. Codependence is an important clinical concept that has been vague and perhaps overused to date.

The second section, on families, builds on the issues of codependence and reexamines the literature and data dealing with culture and alcoholism as well. The involvement of the family in the individual's drinking pattern and drinking life clearly becomes an important facet of these patterns. Family therapy and family intervention systems have been found by many treatment programs to be essential to the recovery program. Clinicians need to understand the research and outcome studies that are presented in this section of the book as they begin to weave family factors into their treatment programs.

The third and fourth sections of this volume underscore the need of the clinician to understand the biochemistry of alcoholism. At this stage, most clinicians may not actively consider the role of serotonin (5-HT) in the treatment of the alcoholic patient, but one certainly needs to understand the role of 5-HT in the mechanisms leading to alcohol preference. The clinician also needs to begin to think in terms of understanding and eventually using modalities that may include serotonin-active drugs or serotonin-uptake blockers in an overall recovery program.

The last section presents clinical pharmacological data on the benzodiazepine receptors and the mechanisms and uses of benzodiazepines in withdrawal and treatment programs, as well as data on the uses of lithium for controlling alcoholism. This section concludes with a short but very important discussion of methodological and ethical issues in conducting research with alcohol-dependent subjects.

Taken either section by section or as a whole, this volume is an important addition both to this series and to the general literature on alcohol dependence. Many in the field of alcohol and alcoholism have functioned on intuition and tradition without applying the scientific method to ascertain the important aspects of each approach. This volume challenges the clinician not only to avoid having a totally unitary approach to alcohol treatment but also to understand and use a multimodality approach.

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**In-Patient Treatment for Alcoholism: A Multi-Centre Evaluation Study,** *by Heinrich Küfner and William Feuerlein in collaboration with Klaus Antons, Dieter Feidel, Thomas Flohrschütz, Erwin Hansert, and Manfred Huber. New York, Springer-Verlag, 1989, 377 pp., $88.10.*

This book presents the results of a multicenter alcoholism treatment outcome study. The project consisted of the prospective study of 1,400 alcoholics who were treated in 21 rehabilitation facilities in West Germany. The participating facilities were classified according to type of treatment offered, admission selection criteria, duration of the treatment program, size of the program, and staffing pattern. Therapeutic goals and the treatment environment were characterized to determine how they interacted with patient characteristics to affect prognosis. The patient characteristics that were studied included personality traits, attitudes, consumption patterns of alcoholic beverages and other drugs, demographic status, and perceptions of the treatment.

The most salient findings were the following: 1) No simple formula for determining prognosis at 6 and 18 months could be derived on the basis of combined consideration of subject and treatment variables. 2) The dropout rate from treatment was highest among patients who were in long-term treatment; however, these patients had the best outcome at 18 months. 3) Approximately 10% of the patients met criteria for controlled drinking and were also clinically improved 6 months after treatment. 4) Younger patients generally had a less favorable prognosis. 5) Treatment was cost effective, as indicated by substantial reduction of work absentee days. A wealth of additional findings are presented. Especially interesting are those relating to gender differences, the impact on outcome of therapeutic gains made in treatment, and the relative effectiveness of different treatment modalities.

This study not only presents important new information but also should serve as a platform for future research aimed at delineating predictor variables for prognosis and the dynamic interplay among treatment process variables. One drawback of this project, however, was that measurement was essentially limited to sociobehavioral variables and thus the conclusiveness of the findings must be tempered. Surprisingly, depression was not found to be among the top five *ICD-9* secondary diagnoses assigned to the patients. Perhaps not as surprising but nonetheless noteworthy is the observation that 53% of the patients were continuously abstinent for 18 months after treatment. There is also reason to pause on noting that 72% of the patients who attended self-help groups following treatment remained abstinent; this aftercare modality had the best success rate and was more than twice as effective as psychiatric treatment.

Used as a general guide for determining who can most profit from treatment, the results indicate that at the time of admission the men who were employed, living with their spouse, and psychologically healthy and stable had the best outcome. Women who had the best prognosis were less severely disturbed psychologically, drank less alcohol per week, and were more assertive than women with poor outcomes. For both men and women, a previous history of alcoholism treatment was associated with a poorer prognosis. Generally, the findings illustrate that intact, socially stable, and competent individuals benefited most from treatment.

In summary, the authors are to be commended for this major contribution. The project spans a 10-year period from its inception to preparation of this report. It is noteworthy that the results have not been published elsewhere. The carefully analyzed data contain information that has major importance for improving the delivery of treatment services for alcoholics and ultimately for shaping health service delivery policy.

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## DEPRESSION

**Phenomenology of Depressive Illness: Depressive Illness Series, vol. 1,** *edited by J. John Mann, M.D. New York, Human Sciences Press, 1988, 256 pp., $34.95.*

The title of this book is somewhat restrictive. Although its major focus is the phenomenology of depressive illness, it goes far beyond by including biological aspects as well as treatment recommendations. Nevertheless, its focus on descriptive aspects of depression is very important and certainly reflects the renewed interest of psychiatrists in the United States in phenomenology and classification of mental disorders as exemplified by the ever-expanding series of *DSMs*. Given the past flux in the nomenclature of depressive states and the emergence of newer classificatory systems over the past 25 years, a review of the present state is certainly very timely.

The material of the book is presented in 12 chapters of differing strengths. In the opening chapter Theodore Shapiro and Deborah Weisbrot cover the semantics of depression in an unusual and brilliant fashion, emphasizing how linguistic frames of reference limit our nomenclature of depressive complaints and syndromes. An overly long "life" account of depressive illness is reported in the following chapter. The next chapter, a succinct summary by Elizabeth Charney and Myrna Weissman of the major epidemiologic studies pursued in the 1980s, is clear and informative. It points to the existence of a broader spectrum of disease in untreated individuals than in hospitalized or treated patients. There is no chapter on genetics, although we are told to look for one. The chapter on bipolar disorders by Peter Stokes is excellent and includes descriptions of the high interepisode morbidity of patients with these disorders. The use of anticonvulsants, however, receives somewhat short shrift. Shelley Aarons's chapter on atypical depression is well written and clinically very relevant. Given the various descriptions of this syndrome, this up-to-date summary is extremely useful. The review of affective disorders in childhood and adolescence by P. Anne McBride and Theodore Shapiro is concise and complete. This chapter also highlights the continuities between affective disorders that exist in children and in adults. Other particularly well-written chapters include "Geriatric Depressive Disorders" by George Alexopoulos, Robert Young, and Jonathan Holt and "Depression and Physical Illness" by David Cella and Samuel Perry. These chapters cover areas that are often neglected in books of this type. My only criticism of the chapter on physical illness is the lack of a more thorough treatment of chronic pain syndromes.

Overall, descriptive aspects of depression are well treated in this book. However, biological and treatment aspects, when included, are treated superficially. Perhaps this was the aim of the editor. On the technical side, typographical errors are numerous. This is a very useful book, particularly for the generalist clinician who wants an up-to-date review of the descriptive aspects of the different forms of depressive illness.

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**Hormones and Depression,** *edited by Uriel Halbreich. New York, Raven Press, 1987, 432 pp., $58.00.*

Following an initial phase of description and quantification, the study of psychoneuroendocrinology, or the relationship between emotional and behavioral states and neuroendocrine functioning, is undergoing a period of reflection and reevaluation. This volume arose from a symposium held by the American College of Neuropsychopharmacology in 1984, and it provides a useful review of both the current status of knowledge and the difficulties associated with future advances in this area of investigation. Several of the chapters contain reviews that overlap with the authors' contributions to other publications. Despite this seemingly inevitable replication, the volume remains valuable because it is thematically well coordinated and because it provides the reader with convenient access to a wide range of related topics. Although the hypothalamic-pituitary-adrenocortical (HPA) axis receives appropriate emphasis, considering its status as the most extensively studied endocrine system in depression, there are also several informative reviews of the thyroid axis, gonadal steroids, and hormonal responses to various pharmacological agents.

The introductory chapter, which is authored by the editor, contains the first of several critical reviews of the "window into the brain" approach to the study of hormonal changes associated with depression. Dr. Halbreich also comments on the problems encountered in the interpretation of "confounding" factors and ends with a plea for acknowledgment that, despite their difficulties, multidimensional paradigms will be essential for future studies. Although some of the author's proposals cannot yet be adequately tested, this is a thoughtful examination of many concerns that currently limit the applicability of psychoneuroendocrine studies in clinical psychiatric research.

The contributions by Reichlin and Rose address the continuing challenge presented by the interface between the physiology of stress and the biology of depression. Early attempts to distinguish the changes seen in depression from "mere" stress responses have been replaced by the recognition that these pathophysiological processes are likely to be intertwined in a crucial and ongoing interaction. This continues to be an important area for future study, and these chapters provide the reader with a summary of current knowledge.

Meltzer reviews the contributions and limitations of the use of neuroendocrine challenge tests in the study of monoamine receptor abnormalities in depression. Examination of the endocrine responses to a pharmacological challenge is a widely used strategy in the study of altered central neurophysiology associated with psychiatric disorders and is central to the "window into the brain" approach. This chapter gives appropriate emphasis to the confounds that must be considered in the interpretation of data obtained by these methods.

An entire section is given over to the HPA system in depression. Several authors critically examine the conceptual models and assumptions that have supported previous research in this area and outline new directions that might be fruitful. The reviews of the clinical applications of the dexamethasone suppression test and the history of studies using corticotropin-releasing hormone probably contain little information that has not been summarized elsewhere, but the topics belong in this volume and are clearly presented.

The concept of the "window into the brain" is examined more closely in several chapters that focus on the effects of neuropharmacological probes on neuroendocrine functioning. Janowsky et al. restate the underlying assumption of the psychopharmacological bridge strategy that has served as the conceptual basis for much of this research: "If a given drug has specific neurotransmitter altering effects in animals, and at the same time has specific behavioral effects in man, there may be a causative link between the two observations." This is followed, however, by a critical review of strategies based on the interaction between a single drug and neurotransmitters in neuroendocrine studies of pathophysiology in mood disorders. As is noted by several authors, the inclusion of a longitudinal design is a key component for future studies of these phenomena.

The chapter by Siever et al. contains a systematic and comprehensive review of noradrenergic probes and effects on growth hormone and corticosteroid systems in animals as well as in normal and depressed humans. Their critical examination of the various goals of these studies and the observation that certain directions have faded but others have strengthened provides the basis for their suggestions for future studies.

The section dealing with animal studies and their implications for depression contains a number of chapters that are likely to be of value to clinical researchers looking for concise reviews of related areas of basic research. Unfortunately, the links with clinical depression are largely speculative and brief at this time, but they serve to emphasize the challenge inherent in attempts to link findings from animal behavioral endocrinology with human psychoneuroendocrinology. The chapter by McEwen contains a careful examination of the role of adrenal, thyroid, and gonadal hormones in the mediation of environmentally triggered neural plasticity, and Duman and Enna review the interactions between pituitary-adrenal hormones and central noradrenergic function and question the relevance of these relationships to the link between depression and stress.

Clinical research in psychoneuroendocrinology is an area of biological psychiatry that is at a crossroads and is arguably in need of refurbished conceptual underpinnings. In that context, this book provides not only a review of much that has been achieved but also the basis for thoughtful examination of areas that are likely to prove of value in the future.

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**Dysthymic Disorder,** *edited by S.W. Burton and H.S. Akiskal. London, Gaskell (Royal College of Psychiatrists), 1990, 125 pp., £7.50 (paper).*

This brief volume on the lengthiest of depressive disorders, dysthymia, is the proceedings of an international conference on dysthymia held in London in June 1987. It easily could have become a tower of Babel, reverberating with diverse viewpoints from different countries concerning a heterogeneous syndrome. What emerges instead is a stimulating review and discussion, if not global consensus, on a controversial diagnosis. The book reflects exciting progress made in the past decade in this important, growing area of research. It illustrates the success of *DSM-III* and *DSM-III-R* in facilitating nosologic communication across diverse settings. And it could almost be a *Festschrift* for Dr. Hagop Akiskal, whose prescient papers circa 1980 molded current *DSM* definitions of chronic depression.

Concise chapters are followed by brief panel discussions from the conference. Experts from both sides of the Atlantic offer their views. There are three chapters by contributors from the United States, five from Great Britain, one from Italy, and one from Hungary. After a foreword by the late Max Hamilton, Akiskal recaps his division of primary dysthymias into subaffective dysthymias and character spectrum disorders. The former have a true affective temperament, abnormal REM latency, and positive family histories for mood disorder and tend to respond to antidepressant medication. Character spectrum disorders lack those characteristics. Akiskal hopes that psychopharmacological advances will shrink the pool of medication nonresponders in the future.

The contributors from the United States are recognizable despite the British-style abbreviation of their first names. M.B. Keller and F.M. Sessa offer a lucid discussion of the development and clinical course of dysthymia, particularly focusing on its comorbidity with major depression. They relate interesting unpublished data, rightly emphasizing the paucity of research in this area. R.M.A. Hirschfeld's elegant exposition of personality and dysthymia demonstrates that dysthymic patients and their recovered dysthymic relatives are moody, fearful, introverted, and shy.

Perhaps less familiar to American readers, the European contributors offer at times differing perspectives. One English study, by N. Seivewright and P. Tyrer, compares dysthymia with generalized anxiety disorder and panic disorder and examines the stability of dysthymia over time. In another, D. Murphy and S.A. Checkley studied dysthymic patients at the Maudsley Hospital Emergency Clinic and found partial support for Akiskal's nosology. Both studies have methodological limitations but are valuable for the discussion they evoked from other conference attendees. (Akiskal remarks that physicians and other professionals may constitute a special class of dysthymic individuals.)

G.B. Cassano et al. present an intriguing if slightly diffuse study of social adjustment in dysthymia. Their review of the trait nature of social impairment in dysthymia has not been updated to include subsequent findings (1, 2). Although the biological underpinnings of chronic depression are of great interest, a disappointing chapter on serotonin (5-HT) and dysthymic disorder says nothing specific to dysthymia. Another chapter on senile dysphoria is a tired review that adds little to our understanding of geriatric dysthymia.

D.P. Goldberg and K.W. Bridges offer a wry look at the evolution of depressive taxonomies, including a section entitled "*DSM-III-R, ICD-10,* and All That." A tension builds between the American medical model of dysthymia and the British view that although chronic social problems may cause "a great deal of human misery" (p. 110), dysthymia is a subclinical state. Do American and European psychiatrists see similar patient populations? Z. Rihmer's refreshing chapter, "Dysthymia: A Clinician's Perspective," ends the book with research (including some rather surprising dexamethasone suppression test data) and clinical observations strongly endorsing Akiskal's conceptualization of the syndrome.

*Dysthymic Disorder* is a valuable meeting of good minds. It clearly reviews our evolving understanding of dysthymia and provides signposts for future research. I recommend it to psychiatrists with an interest in mood disorders.

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## BORDERLINE PERSONALITY AND HYSTERIA

**Psychodynamic Psychotherapy of Borderline Patients,** *by Otto F. Kernberg, Michael A. Selzer, Harold W. Koenigsberg, Arthur C. Carr, and Ann H. Appelbaum. New York, Basic Books, 1989, 210 pp., $22.95.*

Rarely does a new book appear that I find so useful I immediately place it on the reading list for my next semester's seminar for psychiatric residents. This book, by Kernberg and his group at the New York Hospital-Cornell Medical Center, Westchester Division, is one of those unusually worthwhile texts for teaching psychotherapy. It is clearly written and outlines the method used by these psychiatrists in their treatment of borderline patients. Since every psychiatrist who works with patients will sooner or later come across individuals with the label of borderline, it is most useful to have a text of this nature at hand to offer guidelines to approach these patients and to understand their mental gymnastics.

Of course, the book assumes Kernberg's object relations orientation, which he has described many times previously, but it leans heavily on the practical application of this orientation rather than on some of his more obscure theoretical speculations regarding what goes on in the mind of an infant. For this reason, it is possible to understand and apply the techniques of these authors without seriously committing oneself to Kernberg's object relations theory as far as normal and pathological developments are concerned.

The authors treat their patients face to face two or three times a week, and the treatment centers on the perpetual interpretation of the transference. The idea is that each transference dyad contains an object representation and a self representation to which is attached a certain "affectual" charge. In borderline patients the dyads keep changing like scenes in a melodrama. This is an excellent way to conceive of their rapidly changing and often confusing transference manifestations, which produce such confusion and countertransference problems. In addition, the authors offer many practical recommendations with which I agree, such as keeping the focus on the here-and-now as long as the transference remains primitive or, in other terminology, "archaic"; the focus is on what is affectively dominant, not on genetic explanations.

As Kernberg has often explained elsewhere, the goal of the early phase of treatment is to enable coalescence of the "part self and part object representations" (p. 91) into more realistic images through interpretation. The therapist "labels" (p. 93) these for the patient. They are kept split, the authors hypothesize, due to the anxiety that would be felt if opposing representations with their affectual charges were felt together (discussed lucidly on pages 98 and 99). As a clinical example, "The therapist may point out how feelings toward the therapist-mother as a hateful, cold witch have been kept separate from feelings of him as a nurturant mother in order to avoid harboring hate for one who is loved—a state that would produce intolerable anxiety" (p. 107). The therapist also traces how this occurs in the patient's interpersonal relationships: "To bring the part self and object representation to the patient's awareness, the therapist often must retrieve them from their projected locations" (p. 107).

The authors outline a clear step-by-step treatment approach. This will have considerable appeal to psychotherapists in training. There are diagrams and case vignettes to add additional clarity. The book begins with a presentation of *DSM-III-R* criteria, supplemented by a description of Kernberg's concept of borderline personality organization. The murkiest section involves the authors' attempt to apply Racker's work on countertransference, and the neophyte may have trouble with their proclamation that "the therapist who has difficulty with concordant identification intensifies the complementary identifications" (p. 80) as well as the brief examples that are provided in the same paragraph and the next two paragraphs. The neophyte may also be confused or misled by the introduction of "symbolic transfer of the conflict into the realm of the physical and biological" (p. 171), which is, to say the least, controversial and not really discussed by the authors.

Among their excellent clinical comments the authors point out how acting out is highly gratifying and tends to perpetuate itself in patients with borderline personality disorder and how heavily invested such patients are in sacrificing their lives while ignoring what they are doing to themselves. There is an aggressive force—an internal enemy—in the patient's mind, and "the patient is tempted to collude with this internal enemy to avoid a justified fear of that threat from within" (p. 173). Chapter eight, on suicidal behavior, threats to quit treatment, and lying, is especially useful for clinicians.

The book suffers only from a rather uncritical acceptance of certain Kleinian concepts, which reaches its apogee on pages 138–141. Kernberg has a tendency to select those Kleinian concepts which he likes and ignore the rest, making the whole theory more acceptable to those psychiatrists who do not like some of Melanie Klein's more far-reaching speculations. It is possible, however, to use this book in practical clinical work without becoming entangled in either Klein's or Kernberg's theoretical preconceptions, and that is its main value.

In conclusion, I would say that out of the many, many texts on the patient with borderline personality disorder available today, this is probably the best one for the psychotherapist in training and for the clinician who wishes to read about some clear fundamental pointers on how to conduct the psychodynamic psychotherapy of such patients, without having his or her mind cluttered up by speculations, doubts, opposing theories, or alternative methods.

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**My Work With Borderline Patients,** *by Harold F. Searles, M.D. Northvale, N.J., Jason Aronson, 399 pp., $45.00.*

Over the years, Harold Searles has provided us with some of the most profound and comprehensive contributions to the psychotherapeutic approach with both schizophrenic and borderline patients. I therefore approached the present volume with high expectations, and it never let me down. It contains a thoughtful, clear description of a seasoned psychotherapist's experience. Searles's psychoanalytic frame integrates a sophisticated conception of the pathology of internalized object relations with a theory of technique based on transference and countertransference analysis. His theoretical roots include psychoanalytic ego psychology, British object relations theories, and American interpersonal psychoanalytic approaches. Beyond these various influences, Searles presents a highly original contribution to psychoanalytic psychotherapy derived from his own long-standing experience with intensive psychotherapy with psychotic and severe personality disorders.

Perhaps the most central concept in Searles's formulations in this book is the idea that borderline patients, by means of projective identification, project their pathogenic introjects onto therapists, who, in turn, in experiencing the consequences of these projective mechanisms in the countertransference, tend to activate, as part of the countertransference regression, their own primitive dissociated introjects. The condensation of projected transference elements (the patient's introjects) and the therapist's reactivated transference dispositions (the therapist's own primitive layer of pathogenic introjects) permits therapists to identify with experiences that patients cannot tolerate in themselves and to share with patients their understanding of the nature of these primitive introjects. In interpreting the transference, therapists share with patients aspects of the countertransference that reflect their understanding and acceptance of this joint world of projected and reactivated introjects.

On the negative side, Searles adds, the danger exists that therapists may not be able to tolerate the reactivation of their own past introjects within the countertransference. This may lead to premature interpretations of the transference and a consequent perpetuation of projection and reprojection by interpretation, leading to stalemates in the treatment. Another negative possibility is that therapists may become fixated in their own countertransference regression and fail to extricate themselves interpretively from that situation.

Searles warns against the danger of "brainwashing" patients with premature interpretations, but he also refers to the temptation of patients to project their own brainwashing tendencies onto the therapist. He stresses the need for the therapist to accept the countertransference consequences of the patient's transferences as an indispensable precondition for the patient's eventual acceptance of the therapist's interpretations. Searles offers abundant clinical evidence throughout this book to illustrate his proposal that every bit of psychopathology in the patient has a counterpart somewhere in the therapist's functioning and that there are always nuclei of real intuitions in the transference developments.

Another, related central concept is that of the therapeutic symbiosis as an indispensable precondition for psychotherapeutic work to proceed. Searles's concept of symbiosis is a relatively broad one, including both actual merger phenomena (such as are characteristic of transference regression in schizophrenic patients) and those confusions or interchanges of aspects of their personality which are products of projective identification operating mostly in the patient but also in the therapist. In fact, Searles might be overextending the concept of symbiosis, blurring to some extent the distinction between psychotic and borderline transference developments. His clinical illustrations, however, map out unmistakably the symbiotic relationships he has in mind.

The therapeutic symbiosis, in Searles's view, includes the patient's multiple identifications with self and objects, projected and introjected, and is characterized by profound ambivalence because of the mutually contradictory nature of these identifications. This ambivalent symbiosis serves both as a defense against threatening primitive aggression associated with the relationship to pathogenic introjects and as a potential for emotional growth as tolerance and working through of these mutually split-off internalized object relations are achieved in the transference experience and analysis. Searles illustrates the many and complex forms these transference-countertransference developments may take. For example, the patient's defensive detachment as the therapist's vacation approaches may reflect, in part, the patient's identification with the analyst's defensive detachment because the latter cannot fully acknowledge his or her own dependency on the patient. The patient's narcissistic withdrawal, therefore, interacts with the analyst's defenses against the analyst's own dependency needs toward the patient as a transference object. Or, perhaps, oedipal-triangular relationships may be played out by the patient's jealousy of a thriving plant in the therapist's office. At times the therapist who feels "irrelevant" to the patient may represent the patient's projected "irrelevant" self. The therapist, in short, may become the patient's self, his or her multiple introjects, live and dead, human and nonhuman.

Searles reminds us of his earlier work regarding the differentiation of the animate and inanimate world on the basis of the normal introjection of mother during the symbiotic period of development; he points to the deepest levels of loss of orientation toward external reality when the most primitive maternal introjects are split-off and projected.

Searles questions some standard assumptions of psychoanalytic psychotherapy, such as the autonomous development of the "real" relationship to the therapist in the early years of treatment. He points out that this "real" relationship more often than not may be a split-off, symbolically meaningful transference relationship that differs from other, dissociated, transference relationships: the "real" relationship can emerge only in advanced stages of the treatment as the consequence of working through split-off, primitive object relations in the transference.

In an attempt to provide some general characteristics of Searles's technique, I would stress his emphasis on the communication of countertransference; his very careful and gradual development of transference interpretations against the background of the tolerance and silent analysis within the therapist's mind of the symbiotic relationship; a general tendency to tolerate lengthy silences; a long-range time frame for giving patients the "space" to experience themselves as different from the therapist in the relationship, to gradually hear more realistically what is being said, to listen to it, and to associate to it; and the therapist's parallel process of growth in the capacity to hear, listen, and understand. Searles's emphasis, that one can interpret only within the symbiosis—to do otherwise is to risk sterile intellectualizations—is the counterpart to his stress on the therapist's need to tolerate split-off internalized, projected object relations from the patient in the therapist's countertransference before interpretation can proceed.

Searles, I think, tends to underemphasize the differences between psychoanalytic psychotherapy and psychoanalysis proper, in the tradition of the British Middle Group and interpersonal psychoanalysis as contrasted to ego psychology and Kleinian analysis. Searles's contributions to countertransference analysis are, together with Heinrich Racker's work, most important tools for countertransference analysis with severe personality disorders, the psychoses, and severe regression in all cases. His understanding, for example, of the patient's impulse to drive the therapist "crazy" and the transference implications of this development is a classic in this field.

One might raise a question, however, as to what extent Searles's technique, particularly in the hands of less experienced psychotherapists, may foster acting out of the countertransference and a consequent regression in the psychotherapeutic symbiosis beyond actual therapeutic needs. Searles emphasizes the need for the therapist to internalize unconsciously the patient's psychopathology in order to foster its resolution, and he criticizes the tendency of "classical" analysts to maintain themselves separate from the therapeutic symbiosis. In my experience, this tendency applies more to work with psychotic patients than with borderline patients; on the other hand, some stalemates in intensive psychotherapy with borderline patients relate to the therapist's failure to provide a boundary of reality for the patient.

At the same time, Searles's description of the artificial distancing in the psychotherapy that may be caused by the therapist's defensive avoidance of the symbiotic relationship (in the broad sense in which he uses the term) is very well taken. In this context, Searles makes the interesting observation that "autism in the transference" may sometimes reflect the enactment of oedipal jealousy, an unconscious effort on the patient's part to see that the two parents never be alone together. Nonrelatedness, of course, also frequently reflects an identification with an unavailable parent.

Searles explores the very limits of the psychotherapeutic relationship in proposing that the patient can abandon his or her illness only if the therapist has come to cherish it too, so that the patient's improvement becomes an experience of loss for both patient and therapist. This idea touches on some of the most complex and subtle aspects of the developments in long-term treatment of severely regressed patients. Searles also suggests that, just as therapists must become patients' mothering shields against the outside world—so that patients can submerge themselves protectively within therapists—therapists must be able to submerge themselves in patients. Patients thus assume the function of the maternal shield for therapists as a precondition for abandoning the autistic stance. In other words, within the therapeutic symbiosis, patients, by identification with the therapist, must accept their roles as both the protected infant and the protective mother who helps them to differentiate and individuate.

Searles's focus on the importance of facial expression as a direct revelation of unconscious thoughts and feelings is of great interest for its connection with contemporary research on early development and psychopathology of affect. The patient's unconsciously identifying with the analyst's facial expression is a reflection of an introjection of a primitive object. Facial expressions of the patient and the therapist acquire a function in the transitional field that permits mutual identifications and expresses the tolerance of primitive affect in both of them. Searles criticizes Kohut's focus on mirroring as being linked exclusively to the mirroring of loving feelings. Therapeutic mirroring, Searles suggests, includes also the mirroring of the aggressive aspects of feelings: the experience and tolerance of facial expressions of aggression are indispensable aspects of symbiotic regression and eventual individuation, the opposite of the implicitly patronizing attitude of an eternally even-tempered and friendly therapist. Patients read their own emotions in the therapist's face as well as the emotions of the therapist, and the same holds true for the therapist.

Searles's openness, his nondogmatic approach to his subject, and his use of himself to illustrate the need for the therapist to accept pathology as well as continuing growth in himself and in his patient are refreshingly direct ways of opening to the reader the subtle, moving, and inspiring work of a pioneer and leader in this field. There are, of course, alternative approaches to the intensive psychoanalytic psychotherapy with borderline patients. The differences between various strategies of treatment still need to be investigated empirically.

Our own group at the New York Hospital-Cornell Medical Center, Westchester Division, is in the early stages of the empirical investigation of a psychodynamic psychotherapy with borderline patients that, in its general lines, is commensurate with Searles's approach, although substantial differences also exist. We think it is possible to carry out interpretive work very early in the treatment of borderline patients and, using a more restrictive concept of symbiotic transferences (which refers only to merger phenomena in psychotic patients), do not necessarily limit interpretive work to regressive phases of the treatment. Also, although my own approach to the use of countertransference owes much to Searles's work, I would probably be more restrictive in direct communication of countertransference observations to the patient. These differences, however, seem minor in the light of the emerging consensus regarding major strategies derived from psychoanalytic object relations theory applied to the intensive psychotherapy of borderline patients.

Harold Searles's book is a fundamental contribution to this field, and I heartily recommend it to all psychotherapists interested in the intensive psychotherapy of these very difficult patients.

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**Perspectives on "Hysteria,"** *by Phillip R. Slavney. Baltimore, Johns Hopkins University Press, 1990, 190 pp., $24.00.*

Last things first. In his two-page concluding chapter Dr. Slavney writes that this provocative monograph "could well be the last book with hysteria in its title written by a psychiatrist." His justification is that this anachronistic term fails to identify an entity. However, hysteria phenomena "are clinical realities, and their diagnostic recognition cannot be dismissed as ignorance or arrogance." So far, so good, but in the 190 preceding pages, the author and I sometimes part ways.

Dr. Slavney briefly recounts the history of hysteria, then describes several modern perspectives—as disease, behavior, dimension of personality, and a life story. He rejects the term "Briquet's syndrome" (also known as somatization disorder) because its proponents have demonstrated no "broken part." Its adherents knew this all along, he says, although this assertion is repeatedly contradicted in the writings of Guze and his Washington University colleagues. Dr. Slavney often returns to the concept of the broken part without ever defining exactly what it means. He seems to assume that, because pathological changes have not been demonstrated, they do not exist. However, I grant him the valid criticism that Briquet's syndrome has focused too exclusively on the complaint while ignoring the complainer.

For Dr. Slavney, hysteria is not something a person has but something a person does. It is best understood from the perspective of the individual's life story. An interesting feature of this volume is the author's retelling of Anna O.'s history, as interpreted by Breuer and Freud and by Hollender. Dr. Slavney cautions us to inquire carefully into the patient's background and not to impose our own theoretical constructs onto the material: "The substitution of dogma for detail is likely to impede, rather than assist, the formation of psychotherapeutic relationships."

This volume embraces a number of virtues often absent in medical writing. The prose is more than competent; at times, it sings. There are several excellent patient histories, including one of the best case studies of Briquet's syndrome I have read. The references are conveniently collected in the back (a few of the more seminal works are somewhat idiosyncratically called epigraphs). There are interesting chapters on sexism in the diagnosis of hysterical personality disorder and on the sick role in hysteria.

I believe, however, that in eschewing somatization disorder as mere metaphor Dr. Slavney throws out both baby and bath water. The baby in this case is the virtue of clear definition; the lack of such definition initially drove Guze and others to create Briquet's syndrome from the chaos of hysteria. Other perspectives on hysteria offer nothing approaching a careful definition of either the individuals or the phenomena to be studied. Until all writers accept the absolute necessity of adequate definition, we are likely still to see many more books about hysteria, a confusing appellation more useful to novelists than to physicians, yet one that continues to outlive its obituarists.

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## OBSESSIVE-COMPULSIVE DISORDER

**The Boy Who Couldn't Stop Washing: The Experience and Treatment of Obsessive-Compulsive Disorder,** *by Judith L. Rapoport, M.D. New York, E.P. Dutton, 1989, 248 pp., $18.95.*

I was not predisposed to enjoy this book. Over the years I have developed a cynical bias against popularized accounts of medical topics, and obsessive-compulsive disorder has garnered so much interest from the tabloids that I did not believe even a respected clinical scientist (and friend) could resist pressure from a trade publisher to "jazz it up." The title didn't help. Further, I was reading for an assignment, and it is no secret that book reviews carry little weight with academic promotion committees. Fears of having to write something polite but honest combined with the pressures of other deadlines to assign *The Boy Who Couldn't Stop Washing* to "otherwise-wasted-airport-time."

Despite my initial misgivings, airport time stretched into home time for a straight read through. This is a wonderful book. The author, chief of the Child Psychiatry Branch of the National Institute of Mental Health, has composed here an engaging arrangement of clinical research observations, richly illustrated and amplified by frequent case anecdotes. Even to one with considerable clinical experience of this illness, the case material, especially the first-person accounts, illuminated by fascinating nuances of obsessive-compulsive disorder, stimulates new lines of thinking regarding mind-brain relations posed by this puzzling illness. Dr. Rapoport treats the subject carefully, starting with clear definitions and distinctions of obsessive-compulsive disorder from other phenomena with which it is often confused. Subsequently, epidemiology, neuroscience, and treatment findings are described in a fashion that is both accessible to the lay reader and accurate. Befitting a scholarly treatment (one that certainly was not necessary to sell the book), historical, religious, and philosophical views of obsessive-compulsive disorder are discussed in an engaging yet documented and critical manner. The engaging nature and accessibility of this book for general audiences, not just physicians, are attested by its having already made several bestseller lists.

For readers with this illness, the detailed and empathetic descriptions of others with obsessive-compulsive disorder will undoubtedly bring relief in the knowledge that the troubling, usually hidden symptoms of the disorder are not only known but understood. This text should be helpful as well for family members of such individuals, who are often baffled or frustrated by the inexplicable behavior in their otherwise understandable relatives. For both groups, hope is provided through descriptions of the relatively new behavioral and drug treatments that have taken obsessive-compulsive disorder from being the major psychiatric illness with the worst prognosis to one of the most treatable. False hopes are not aroused, however, and the failures and limitations of both behavioral treatment and medications are also acknowledged.

This is not a perfect book. The first-person accounts often seem both too insightful and too literate not to have had editorial manicures. I would have preferred the convolutions and ramblings that so often color the writing of those preoccupied by obsessive thinking. I would also be remiss in not acknowledging that many have criticized the book's preference for the trade name Anafranil instead of the generic clomipramine. To those overconcerned with implications of possible commercial ties, I would point out that the author explains the reasons for this preference (patients usually remember the trade name best) and that the critique of the drug is accurate and fair—far different from recent popular news media coverage of another antidepressant agent with anti-obsessional potential.

So much for my biases about the uniform worth of books on medical subjects for lay audiences—*The Boy Who Couldn't Stop Washing* is a model for how these things should be done. I will indulge my personal compulsions and repeat, This is a wonderful book.

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**Treating Obsessive-Compulsive Disorder,** *by Samuel M. Turner and Deborah C. Beidel. Oxford, Pergamon Press, 1988, 117 pp., $22.50; $12.95 (paper).*

Coincident with the current explosion of scientific and popular interest in obsessive-compulsive disorder and aided by the work of organizations such as the Obsessive-Compulsive Foundation of New Haven, Conn., increasing numbers of patients are coming to clinicians seeking treatment for what they themselves have identified as obsessive-compulsive disorder. In my experience, this often seems to raise anxiety in psychiatrists—for understandable reasons. Despite the prominent role this illness played in the development of classical analytic theories of "neuroses," obsessive-compulsive disorder is quite resistant to traditional psychotherapies and psychotropic medications and, until recently, seemed, thankfully, rare. Most psychiatrists have had little direct experience with patients with obsessive-compulsive disorder (in my residency, 1978–1982, I treated one), and the treatments with documented efficacy are drugs that were not available in the United States before 1990 and behavioral therapies that most psychiatrists have been content to leave to their psychologist colleagues.

There is a great need at present, therefore, for reliable and effective instruction on the treatments of choice for obsessive-compulsive disorder. *Treating Obsessive-Compulsive Disorder* is a helpful addition to what is a scant practical literature. The authors are with the Anxiety Disorders Clinic at Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine.

The book starts appropriately with a good description of the clinical syndrome, followed by a discussion of the differential diagnosis. The differential diagnosis of obsessive-compulsive disorder is important because many patients—and far too many psychiatrists—confuse preoccupying depressive ruminations, psychotic rituals, certain specific phobias, and non-ego-alien disorders of impulse control (e.g., "compulsive shopping") with obsessive-compulsive disorder, and the appropriate treatment of these maladies is often quite different.

Chapter three deals with assessing the patient, especially in the light of several common patterns of treatment resistance. This sets the stage for what is the most valuable part of the book, chapter four, which describes behavioral treatment of obsessive-compulsive disorder based on the principles of exposure and response prevention, and chapter five, "Implementing Behavioral Treatment Strategies." Although much of chapter four is a rather standard, although unusually clear, description of methods and some of the data validating them, I found the most valuable section to be one entitled First Person Description by Mrs. C, where a patient describes her subjective experiences in the course of treatment. This is particularly valuable because it illustrates that the key to successful behavioral treatment of patients with obsessive-compulsive disorder is not just an understanding of exposure and response prevention but, rather, working with the patient in a way that makes the patient willing to apply this understanding. This is not an easy feat, and empathy for the plight of a patient confronting such powerful emotional forces is vital. Chapter five goes on to give five case examples, followed by model treatment plans and comments directed at the specific nuances of the case situations.

Chapter six, which deals with biological treatments, is the weakest in the book. Perhaps due to the date of writing (the field has moved rapidly, and even 1988 seems ancient) or to the orientation of the writers (both have doctoral degrees and the book is in the Psychology Practitioner Guidebooks series of Pergamon Press), the description of pharmacotherapies is thin. This is to be lamented. There was enough of a literature on clomipramine at the time the book was put together to have allowed practical information on the clinical use of this drug. There is, in fact, a fair summary of the experimental work documenting this drug's efficacy. Now that clomipramine has been released in the United States, and several other drugs that may also be effective in obsessive-compulsive disorder are either available or soon will be available, there is a clear need for a text that not only describes the use of these agents but also discusses how they can be integrated with behavioral therapy to provide the most effective management for the patient with severe obsessive-compulsive disorder.

The final chapter deals with maintaining treatment-induced improvements. There is little rigorous systematic research in this area, and the discussion must be read in this light, but I did find the authors' comments interesting.

On the whole I think this is a valuable book, especially for those seeking a brief, practical guide to the behavioral management of obsessive-compulsive disorder. I have already recommended it to several colleagues, all of whom have commented favorably.

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## SOCIAL ISSUES

**Medical Marriages,** *edited by Glen O. Gabbard, M.D., and Roy W. Menninger, M.D. Washington, D.C., American Psychiatric Press, 1988, 177 pp., $28.95.*

This book arose from 10 years of experience running an annual 6-day summer workshop for physicians and their families. Although medical marriages are vulnerable to the same pressures as other marriages (individual character structure, unrealistic expectations of each other, divided loyalties, financial strains, double careers, diverging developmental paths, midlife stress), some aspects of the medical marriage are unique. Different chapters in this book address various perspectives on physicians and their intimate relationships. Most physicians and most spouses of physicians will find something in the clinical vignettes with which to identify, and most will want to ensure that their partners not only read but take to heart certain pages.

For the most part, the chapters deal with the so-called "traditional marriage"—a marriage between a hard-driving, dedicated, wage-earning male physician who commands the respect of the community and the attention of forever younger female medical colleagues and his long-suffering stay-at-home wife who cares for the children, the parents, the social engagements, and the comforts of bed and board. For older physicians, the "traditional marriage" remains a problematic reality. Fewer and fewer medical marriages, however, fit that mold today. Contemporary physicians are often women (whose particular issues are addressed in two chapters by Malkah Notman and Carol Nadelson); most physicians nowadays enter into dual high-powered career marriages; physicians' marriages—like everyone else's—are now multiple; and the impact of new physician-specific stressors (the potential spread of AIDS in the workplace, "managed" care delivery systems, health technology, malpractice threats, the changing status of the physician in the community, and increasing awareness of bioethical dilemmas) has the potential of severely disrupting the home life of physicians. These contemporary issues are not specifically addressed.

There is much to learn in these pages, nevertheless. Domeena Remshaw's chapter on sexual problems in physician couples illustrates, frighteningly, how physicians try to treat themselves rather than seek qualified opinions. Physicians find it difficult to accept the need for marital therapy or individual psychotherapy. Serious depression, family dysfunction, and substance addiction may go untreated. Work hours may rise exponentially at the expense of quality of life. If the unexamined life is not worth living, then a failure by physicians to consider seriously the issues raised in this book potentially undermines the value of their closest relationships.

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**Contemporary Perspectives on Psychotherapy With Lesbians and Gay Men,** *edited by Terry S. Stein, M.D., and Carol J. Cohen, M.D. New York, Plenum, 1986, 263 pp., $29.50.*

This is not a book about treating homosexuality but, rather, a collection of fine chapters by well-known experts focusing on the unique and often misunderstood problems of providing psychotherapy to patients who happen to be lesbians or gay men. Although homosexuality per se was dropped from APA's *Diagnostic and Statistical Manual of Mental Disorders* in 1973 it has still taken 15 years for two psychiatrists to edit a book informing us about some of the special problems faced by this now recognized minority group.

That does not mean that more papers have not been written and given, it just means there has been a problem in getting the work published in mainline journals and books. Some of the old bias still seems to cling, and in the first chapter of this book James Krajeski eloquently describes the history of the controversy. The next chapter, by Drs. Stein and Cohen, establishes the three major assumptions of the entire work: 1) homosexuality per se is not associated with psychopathology, 2) sexuality has enormous clinical relevance within psychotherapy, reaching well beyond a single feeling or act, and 3) in our society men and women experience their homosexuality in different ways, largely as a result of the distinct gender role socialization patterns within which boys and girls are raised.

The book has a scholarly balance attending to the special differences between lesbians and gay men. A version of Richard Isay's chapter on analytic therapy for gay men was originally published in *The Psychoanalytic Study of the Child* (1); it offers a controversial and at the same time more understandable theory of homosexuality in men that is not encumbered by the pathology model. Far too many analysts persist in the treatment of homosexuality, forgoing scientific outcome studies on the effectiveness and efficiency of the treatment.

Individual chapters on group therapy for gay men, special issues for lesbian mothers, and a description of the experiences of a pregnant lesbian therapist bring a personal authentic flavor to the work.

A chapter on working with patients with HIV disease is written by Stuart Nichols, one of the earliest psychiatrists to recognize and begin to prepare for the almost overwhelming psychiatric needs of individuals with HIV infection and those surrounding them.

This book is a long overdue and very welcome addition to our therapeutic knowledge and skill, especially in our work with minority groups. All psychiatrists see lesbians and gay men in their practices, and all should have the special knowledge and tools that *Contemporary Perspectives on Psychotherapy With Lesbians and Gay Men* offers.

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**The AIDS Bureaucracy: Why Society Failed to Meet the AIDS Crisis and How We Might Improve Our Response,** *by Sandra Panem. Cambridge, Mass., Harvard University Press, 185 pp., $22.50; $9.95 (paper).*

The body of this book is a very generalized, vaguely referenced chronicle of some of the interactions of the various government agencies during the early part of the AIDS epidemic. Compared with the dynamic work *And the Band Played On* by Randy Shilts (1), it is uninteresting and uninformative.

The conclusion of the text, "Lessons for the Future," is not insightful, nor would it improve the poor results of the sluggish U.S. bureaucracy that has yet to organize any substantial productive research on AIDS. Most of our advances thus far have resulted from the ambitions of individual scientists with marginal and late funding from the federal government. In addition, each research group competitively conceals its data from the other groups, additionally hindering the advancement of the overall research effort.

The government bureaucracy that has mismanaged the AIDS epidemic is much more complex than described in this book. Furthermore, the major reason that a centrally organized "Manhattan Project" has not been formed to address the problem is the severe homophobia and warped puritanical attitudes of the U.S. government and people. If AIDS were only a heterosexual problem, with 1–2 million infected young, productive heterosexuals, 140,000 cases of heterosexual AIDS, and 75,000 heterosexual deaths, the AIDS bureaucracy would be responding in a dynamically different, rapid manner with virtually unlimited resources and a centralized, noncompetitive scientific research program. That is the bottom line, and this text completely misses it.

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**Psychiatry Takes to the Streets: Outreach and Crisis Intervention for the Seriously Mentally Ill,** *edited by Neal L. Cohen. New York, Guilford Press, 1990, 306 pp., $40.00.*

Edited books are often motley collections, but this book is more motley than most. Its title and cover, with a picture of a homeless woman, are distinctly misleading because they seem to promise a book about outreach programs for the homeless mentally ill. Only a small portion of one of its 15 chapters, however, is about such a program—the Homeless Emergency Liaison Project operated by Gouverneur Hospital on the Lower East Side of New York City. One other chapter (by Kostas Gounis and Esra Susser) is about problems encountered in establishing a psychiatric program in the Franklin Avenue Men's Shelter in the South Bronx and is in fact one of the more interesting chapters. Except for these two contributions, the homeless are nowhere to be seen in this volume.

The largest number of chapters describe mobile crisis units that visit patients in their homes. The title *Psychiatry Takes to the Streets* apparently refers to taking to the streets as a means of reaching patients in their homes. Thus, the well-known Thresholds Bridge Program in Chicago with its assertive case management is described, as well as lesser known but laudable programs such as the Community Support Treatment and Rehabilitation Program in Baltimore, the Greater Bridgeport (Conn.) CMHC Mobile Crisis Team, and the Spokane CMHC Elderly Services Program. Psychiatric professionals interested in assertive case management and mobile crisis units will find such chapters of considerable interest. The best chapter of all, however, is Martin Fleishman's well-written and practical account of his 22 years as a mobile psychiatrist to board-and-care homes for the mentally ill in San Francisco.

The book has abundant shortcomings. A chapter about the advantages of psychiatric home visits never even mentions Benjamin Pasamanick's Louisville Project, the most extensive research on psychiatric home visits yet carried out. The chapter on New York's Homeless Emergency Liaison Project outreach to the homeless mentally ill never mentions the Joyce Brown (Billy Boggs) case or the hotly debated civil rights issues engendered by such programs. Nor is this issue addressed by the mobile crisis units, and the reader is left wondering what is meant when, for example, Annelle S. Primm and Jane Houck of Baltimore's Community Support Treatment and Rehabilitation Program say that "patients are pursued by staff so that medication levels can be maintained."

With the exception of Thomas F. Witheridge's chapter on the Thresholds Bridge Program, which has been a model of data collection and self-assessment, virtually no data are presented that can be used to justify mobile crisis teams or home visits. Where are the cost-benefit studies? There is a final chapter on using "a developmental approach" to engage treatment-resistant young adult chronically ill patients. These patients, three-quarters of whom have schizophrenia or bipolar disorder, are said by the authors to have "a deficit in object constancy," and they outline a psychoanalytic approach based on the writings of D.W. Winnicott, Margaret Mahler, and others. Such a chapter in a volume on outreach is not only anachronistic but bizarre when juxtaposed, for example, to Fleishman's very practical advice on the advantages of personally giving intramuscular injections to patients so that "the psychiatrist's nose comes in close proximity to armpit and crotch, and as such affords an exquisite appreciation of the patient's baseline with respect to grooming and personal hygiene."

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*Reprints of Book Forum reviews are not available.*

# Letters to the Editor

## Abuse of Potassium by a Patient With Bulimia Nervosa

SIR: Patients with eating disorders often take dangerous risks to rid themselves of food while ignoring the potentially negative consequences of their desperate efforts to lose weight. The use of vomiting and laxatives as purgatives in bulimia nervosa has been well described (1, 2), but little has been written about patterns of diuretic abuse (3). This report discusses the effect of ingesting potassium on a patient who took it thinking it could act as a diuretic.

Ms. A was a 39-year-old woman who had a 3-year history of bulimia nervosa with daily vomiting and borderline personality disorder with severe mood swings. Her medications were fluoxetine, 100 mg/day, and lithium carbonate, 600 mg/day. The high dose of fluoxetine was prescribed because of the severity of her binge eating and purging (previously, several times daily) and her lack of response at lower doses (2). While reading a popular nutrition book (4), Ms. A came across the following statement: "Since a lack of potassium allows sodium and water to pass into the cells, increasing the intake of this nutrient often corrects edema, or water retention" (p. 192). The patient understood this to mean that the ingestion of potassium chloride could serve to reduce water retention. (Potassium actually has no significant diuretic effect.) She began taking approximately 1 tablespoon per day (70 meq) of a commercial salt substitute composed of potassium chloride. On the fourth day of this regimen, Ms. A admitted to taking 3 tablespoons (200 meq) of potassium because she felt bloated and panicked after eating a large amount of salted nuts; however, the actual amount ingested may have been greater, and this may have accounted for the effects observed (3).

Shortly after this ingestion of potassium chloride, Ms. A came to the emergency unit with recurrent paresthesias in her extremities, neck and facial muscle stiffness, and abdominal cramping. She denied suicidal ideation and knowledge about the potential toxic effects of potassium overdose. The results of physical and neurological examinations were unremarkable. Laboratory findings revealed that her serum potassium level was 7.3 meq/liter, and her phosphate level was 1.1 mg/dl, but all other values were within normal limits, including renal functions (creatinine was 0.8 mg/dl, BUN was 9.0 mg/dl) (3). An ECG revealed normal sinus rhythm, with peaked T waves in the precordial leads, and first-degree atrioventricular block (PR= 0.22 seconds). The QRS complexes, however, were of normal duration. Drug levels at the time of admission were not ascertained, but levels several months earlier had been found to be those for the prescribed doses (2). Ms. A was treated with one ampule of calcium gluconate, one ampule of 50% dextrose in water, intravenous normal saline, and three oral doses of sodium polystyrene sulfonate. This led to the subsequent resolution of her symptoms (her serum potassium level was 4.2 meq/liter) the following morning.

This patient presented with hyperkalemia after ingesting a large amount of potassium. Normally, the kidneys can closely regulate potassium homeostasis; however, when potassium is taken in large doses, transient hyperkalemia can result (5). This hyperkalemia has no significant effect on renal function, but it can have serious cardiac and neuromuscular effects (3).

Patients with eating disorders often report extreme anxiety after the ingestion of high-calorie foods and take considerable risks to rid themselves of the bloated feeling. In this case, hyperkalemia was the near-fatal consequence after the patient ingested potassium, having received the false impression that it had a diuretic effect. Although hypokalemia is a more frequently reported effect of purging behavior, patients may also increase their intake of potassium because of misinformation and their desperate attempts at weight control. We suggest asking direct questions about the use of salt substitutes when patients with eating disorders are found to have high levels of potassium (4).

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## Real-Life Basis for a Patient's Paranoia

SIR: As part of a prospective study of the psychobiology of first-episode schizophrenia (1), we evaluated an unusual case that was handled in the psychiatric emergency room of our facility.

Ms. A, a 31-year-old unmarried woman, was brought to the emergency room by a counselor from the patient's workplace who was concerned about her recent erratic behavior, including deterioration in her work performance and her fear of remaining on Long Island after 8:00 p.m. The patient had been evaluated initially by other staff members and found to have a "psychotic disorder not otherwise specified" of recent origin, with a prominent paranoid delusional system involving fears that the Mafia and police monitored her every move. Ms. A was offered voluntary hospitalization, but she refused on the grounds that "something horrible would happen" if she was physically on Long Island after 8:00 p.m.; she would not elaborate her fears. However, she agreed to return to the clinic with family members the following morning.

When she returned the next day, we had the opportunity to examine her. We found her to be goal directed and somewhat eccentric. She stated that a certain female friend of hers had been threatening her with severe punishments if she did not abide by her wishes. These threats had been recorded by the patient during a 2-hour telephone conversation, and she brought the recording in to us as "evidence." To our astonishment, the threats were real and included demands that the patient be out of Long Island and at home by 8:00 p.m. She was to be at the beck and call of this woman. The family confirmed the sadomasochistic-like relationship of the patient and her friend. They said that Ms. A had always had a fragile personality and was easily influenced by others. This friend was indeed a sadistic woman who had an interest in monitoring the patient's activities, although some of the powers the patient attributed to her seemed to be at the edge of credibility.

Ms. A was persuaded to enter the hospital for a period of observation. The tape-recorded telephone conversation was eventually listened to in its entirety, and it confirmed that bizarre threats to the patient had been made by this woman. To date Ms. A has displayed no other unusual ideas or schizophreniform inclinations.

This case demonstrates some of the "gray" psychosocial and diagnostic areas in psychiatry. The possibility of a *folie à deux* cannot be totally ruled out in a patient with certain premorbid personality characteristics (i.e., dependency, paranoia) (2). Nor can it be definitively said that this was not the initial presentation of a prodrome of eventual schizophrenia. However, this case should also serve to remind us that occasionally, when someone enters an emergency room with a paranoid belief system, the unbelievable can be the result of a valid life situation.

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### Tardive Dyskinesia in a Patient Taking Haloperidol and Fluoxetine

SIR: I wish to report the development of tardive dyskinesia in a man treated with low doses of haloperidol for brief intervals and fluoxetine.

Mr. A was a 39-year-old man who had a history of episodic paranoia. His first paranoid break had occurred 10 years earlier and was accompanied by depressive affect and an overdose of diazepam. The patient had been hospitalized for 10 days and treated with an unidentified antipsychotic medication, which he did not take after discharge. He remained symptom free for the next 10 years, during which time he began to use alcohol, up to five drinks a day, to deal with anxiety and obsessional worrying about his job. He was then admitted to a general hospital because he was acutely intoxicated, paranoid, and delusional. Unmanageable on a chemical dependency unit, he was transferred to a psychiatric hospital where he was detoxified and treated with haloperidol, 5 mg/day, to control his paranoia. He was discharged on a regimen of haloperidol, 4 mg/day, which he took from January until the end of March. The dose was then lowered to 1 mg/day until the drug was discontinued in November. Fluoxetine, 20 mg/day, had been started in February, and it was continued, since it treated the chronic anhedonia successfully. Mr. A remained free of neuroleptics from November until the following April, when his paranoia reoccurred. He was again started on haloperidol, 2 mg b.i.d., and the dose was lowered to 1 mg/day in May. In September of that year, during a routine examination, at which time he was free of depression and psychosis, Mr. A complained that his wife had noted episodic puckering of his upper lip, which he felt was a "nervous habit." Examination confirmed the periodic puckering and demonstrated fine vermicular movements of his tongue. Tardive dyskinesia was diagnosed, and haloperidol was discontinued. Because of the dramatic antidepressant response, fluoxetine was continued, and the patient has been followed closely to monitor his tardive dyskinesia.

It is unusual for tardive dyskinesia to develop with such a low dosage and brief exposure to haloperidol. Baldessarini and Marsh (1) provided data which support the hypothesis that serotonin uptake-inhibiting agents inhibit dopamine neurons projecting from the midbrain and brainstem to the forebrain. Lipiński et al. (2) suggested that akathisia seen in patients taking fluoxetine may be due to down-regulation of dopamine activity. These observations support the hypothesis that the development of tardive dyskinesia may have been facilitated by fluoxetine. I urge clinicians to watch closely for signs of tardive dyskinesia in patients taking low doses of antipsychotic agents combined with fluoxetine.

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### Treatment of Pathological Jealousy by Fluoxetine

SIR: A recent article (1) described the successful treatment of a pathologically jealous patient by fluoxetine. I wish to report a similar case.

Ms. A, a 34-year-old woman, was referred to me by a therapist after a long period of psychotherapy because of the worsening of her intense jealousy of her husband since the birth of her second child. Throughout her marriage she had been suspicious that her husband was unfaithful, but she had no real evidence. She called him at work many times during the day. If the telephone line was busy, she was sure that he was talking to a girlfriend. She hounded him with questions about his whereabouts and insisted he account for every minute.

Her symptoms went back to childhood, when she had felt that she could not trust anyone. When she first started to date boys at age 15, she "drove them crazy" with her jealousy. She stated that she had never felt at peace and had never felt happy as far back as she could remember.

When asked if she really believed that her husband was unfaithful or whether these were unwelcome thoughts that plagued her, Ms. A replied that she wasn't sure. She reported no vegetative signs of depression, had no complaints of depression, and did not look or sound depressed, but she reported, and showed during the interview, a great deal of anxiety at all times.

The differential diagnosis was between delusional disorder and obsessional disorder. Ms. A met all the *DSM-III-R* criteria for the former: nonbizarre delusions, no hallucinations, no bizarre behavior other than the delusions; and no organic factor or schizophrenia. For obsessive disorder she fulfilled three of the four *DSM-III-R* criteria; the one she did not meet was "the person attempts to ignore or suppress such thoughts." Nevertheless, I tended to favor the latter diagnosis, on the basis of her uncertainty about whether to believe her suspicions, her warm and loving attitude toward her husband despite her suspicions, and the warm, trusting attitude she displayed during the interview.

I prescribed fluoxetine, 20 mg/day, intending to increase the dose gradually. After 2 weeks Ms. A reported, "Things are better; some days good, some days horrible." Because of the considerable improvement, I continued the same dosage. After 4 weeks she reported, "I feel wonderful, ecstatic! I like myself; I like everyone. I haven't felt this good in my whole life . . . . I used to make phone calls all day long; I haven't made a single phone call since I saw you last. It's like being reborn into another person!"

Follow-up over 6 months has shown no alteration of her new feelings about herself and her husband.

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## Familial Trichotillomania

SIR: Trichotillomania denotes recurring inability to inhibit impulses to pull out one's own hair, resulting in noticeable hair loss. Swedo et al. (1) outlined the effectiveness of treatment with clomipramine and noted parallels between the biogenetic phenomenology and treatment responsiveness of trichotillomania and obsessive-compulsive disorder. However, *DSM-III-R* states that familial cases of trichotillomania have not been reported. We present a case of familial trichotillomania.

Ms. A, a 37-year-old woman, sought help for her chronic pulling out and ingesting of her eyebrows and eyelashes. As early as age 6, she had experienced repetitive thoughts and displayed compulsive behavior such as avoiding sidewalk cracks and counting the number of drips from a faucet. As a child, adolescent, and adult she had been a victim of repeated physical and sexual abuse. During the episodes of trichotillomania, which were preceded by an irresistible impulse and followed by a sense of tension release, she would repeatedly pull out her eyebrows and eyelashes and bite her nails to the point of bleeding.

Ms. A has seven sisters and five brothers. One sister repetitively pulls out her eyebrows and eyelashes, and one brother repetitively pulls hair from his head, which results in numerous bald areas.

At initial contact, Ms. A had been treated for depression by her family physician with fluoxetine, 60 mg/day. However, as her mood improved, she continued to pull out hair. Her treatment was changed to clomipramine, up to 100 mg h.s. Over a span of 5 weeks she experienced further improvement in her depression, and her eyelash and eyebrow pulling also diminished markedly. Improvement has continued over 4 months.

Ms. A is typical of other patients with trichotillomania reported in the literature. Coincident with her trichotillomania, she had childhood problems with counting compulsions, which in retrospect met the criteria for obsessive-compulsive disorder. As an adult she did not have obsessions or compulsions. Additionally, she had been repeatedly sexually abused. Since her depression improved and her trichotillomania persisted during treatment with fluoxetine, a neurophysiologic distinction between these two elements of her condition is implied.

It has been reported that fluoxetine is effective in treating kleptomania, bulimia nervosa, obsessive-compulsive disorder, compulsive facial picking, and pathological gambling (2–5). The novel element in this case is the presence of a familial pattern. From a family of 13 children, two sisters and one brother engaged in hair pulling. Ms. A's hair pulling responded positively to clomipramine, consistent with Swedo et al.'s report (1). The coexistence in childhood of depression, obsessive-compulsive symptoms, habit disorder, and trichotillomania suggests that the etiologic factors and the behavioral phenotypes of these disorders may be shared. Repeated sexual victimization may be an experiential trigger (5). Our patient was uncertain whether her siblings had been similarly abused.

This patient's differential behavioral response to medications suggests that the neurotransmitter dysfunctions resulting in these disorders may differ. Since both fluoxetine and clomipramine are potent serotonin reuptake inhibitors, the implication is that the differences may be qualitative.

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## Urinary Retention as a Possible Complication of Long-Term Diazepam Abuse

SIR: The purpose of this letter is to report what we believe is a side effect of diazepam that we have not seen described in the literature.

Mr. A was a patient with a history of opiate dependence (methadone maintenance) since 1972 and a known history of diazepam dependence since 1978, using doses of diazepam in the range of 500–600 mg/day.

In 1978 he was admitted to the hospital twice for detoxification from diazepam and stabilization on a methadone regimen. During a third admission in 1982, the patient complained of frequency of urination, dribbling, and difficulty voiding and was treated twice with 5 mg of bethanechol chloride subcutaneously. Acute urinary retention immediately following that admission led to his readmission to the urology service, where he was catheterized and 800 cc of urine were obtained. Urodynamic studies revealed an atonic bladder for which no organic etiology was found. The catheter was removed after 17 days, and the patient was then able to void on his own.

In 1984 Mr. A was admitted again to the urology service because of urinary retention. Catheterization again obtained 800 cc of urine, and a urine drug screen was positive for opiates and benzodiazepines. A neurologist was consulted but no neurologic cause for the urinary retention was found. Stimulation with bethanechol chloride produced no flow; the detrusor response was absent. Findings of an intravenous pyelogram were normal. Cystoscopy showed areas of erythema thought to be due to catheterization, but there was no other lesion. The prostate and urethra were normal. The patient was taught self-catheterization and discharged.

Mr. A continued to use up to 600 mg/day of diazepam until he was readmitted 4 months later for detoxification. He was detoxified from diazepam and stabilized on a regimen of clorazepate dipotassium, 15 mg q.i.d., because his inability to tolerate complete abstinence led to repeated relapse. He catheterized himself six times a day during this admission.

Between 1984 and 1988 Mr. A was readmitted to the hospital several times, and on each of these occasions he was catheterizing himself six times a day. By late 1988, the dose of clorazepate dipotassium had been reduced to 15 mg t.i.d. He was readmitted for detoxification from clorazepate dipotassium, since benzodiazepine made it impossible to screen for continued diazepam abuse. As the clorazepate dipotassium was reduced and then discontinued, bladder function slowly returned, and the patient discontinued self-catheterization.

When Mr. A first experienced urinary retention, his only prescribed medication was methadone, 60 mg/day; he was also abusing diazepam, 600 mg/day. Between 1976 and 1980 he had received a number of psychoactive drugs, such as doxepin, 50 mg. t.i.d., for several months; short-term treatment with haloperidol, 2–8 mg/day; short-term treatment with perphenazine, 2 mg t.i.d.; and amitriptyline, 50 mg t.i.d., for 2 days. This had been discontinued because he developed acute urinary retention, which promptly responded to 5 mg of subcutaneously administered bethanechol chloride. During this period the patient was abusing diazepam, up to 30 mg/day. By the early 1980s he had considerably increased his diazepam abuse, and by 1982 he was using up to 600 mg/day of diazepam. The urinary retention continued despite methadone detoxification in the mid-1980s.

When Mr. A was finally detoxified from diazepam with the help of clorazepate dipotassium, his urinary retention gradually improved, and he finally regained normal micturition. Thus, there is a strong indication that large doses of diazepam were the cause of his urinary retention, since recovery occurred only after he was detoxified. Since 1989 Mr. A has been receiving trifluoperazine, 2 mg t.i.d., and doxepin, 50 mg t.i.d., without recurrence of urinary retention.

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## Publication and Funding Policies

SIR: Recently, the *American Journal of Psychiatry* returned unreviewed a manuscript that my colleagues and I submitted for publication, because it was considered to be a single case report (see "Information for Authors" in most issues of the *Journal*). In actuality, the manuscript described the first apparently successful psychopharmacologic treatment, with follow-up, of a *series* of three prototypic patients within a single diagnostic category that has not generally been responsive to a variety of therapeutic interventions. Subsequently, the manuscript was submitted elsewhere for review.

As a result of this "rejection," several unscientific hypotheses have occurred to me. 1) If they were written today, the case reports of Sigmund Freud would not be published by the *Journal* except as brief letters to the Editor. 2) Were he with us today, Freud would be unable to achieve academic tenure in most university departments of psychiatry, since his work, although "programmatic," would be unlikely to be funded and supported by the usual, currently available grants. 3) If grant and insurance funding were to become available, a "decade of the mind" might become a possibility, to supplement and coincide with the current "decade of the brain." 4) Some segments of the psychiatric community, perhaps reflecting the larger society, seem to be accumulating knowledge without acquiring wisdom.

In the absence of some changes in our thinking and funding mechanisms, tomorrow's Sigmund Freuds and Karl Menningers will likely be forced to survive apart from university academic settings and will be publishing their cases, ideas, and speculations in periodicals other than the *American Journal of Psychiatry.*

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## Problems With Reports of Preliminary Results

SIR: I am writing to express my concern about the practice of doing preliminary analyses and presenting data from ongoing double-blind studies. While this has clearly been done for many years, it seems to me that APA and its journals, as well as other scientific journals, have some obligation to limit the preliminary publication or presentation of such data. Reports of preliminary results may present a variety of scientific problems. They are incomplete reports of studies usually designed to be conducted with a specified number of subjects, a number usually estimated through power analysis. Thus, preliminary reports are inherently unreliable but are added to the literature in this fashion. Second, such reports may bias participants in those studies as well as other investigators conducting similar research. Third, although statistical methods for correction of this practice exist, they are rarely used. I believe that the standard is to omit the portion of the sample from which these preliminary reports come, but this is, in fact, clearly not done. While the pressure to be "first," the desire to demonstrate the ongoing effort to various granting agencies by publishing or presenting preliminary analyses, and other pressures are understandable, it seems that this is a disservice to science and confounds the efforts to test hypotheses in a statistically and scientifically robust fashion. I suggest that journals which accept papers on studies in which there have been preliminary presentations of the incomplete data set ask the authors to make explicit statements about whether these partial samples are included in the report, at what point (i.e., with what number of subjects) the preliminary analysis was completed, and what statistical compensation has been made for this in the analysis. Establishing such a policy would at least allow the readers of such studies to understand the biases that may have been introduced by these analyses. Finally, it should serve to help even those with the best of intentions to limit or omit this scientifically unsound practice.

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## Manual Versus MEDLINE Searches

SIR: As medical information specialists and experienced MEDLINE searchers in a number of medical disciplines including psychiatry, we read the article by Joseph C. Bareta, M.S., and associates (1) with great interest. Since we are well aware of MEDLINE's deficiencies, we welcome studies that critically evaluate its effectiveness in various disciplines. Reports of such studies constitute an important segment of library/information science literature and serve as a vital impetus for improving MEDLINE. Therefore, it is very troubling to us that an article based on deficient data, faulty methods, and misleading if not false conclusions could have been accepted for publication in a journal as distinguished, highly cited, and influential as the *American Journal of Psychiatry.* The publication of an article such as this misleads psychiatric researchers and clinical practitioners regarding the value and effectiveness of properly executed MEDLINE searches.

Mr. Bareta and associates claimed that the manual search undertaken in their study was markedly more successful in locating articles on consultation-liaison psychiatry than was the computerized search of MEDLINE. We maintain that a properly constructed MEDLINE search might have retrieved almost all, if not all, of the citations the authors retrieved manually, as well as many additional useful citations from other journals. As Cooper (2) indicated, on-line literature searches are a vital step in the preparation of review articles. On-line databases such as MEDLINE are designed to help complete a lengthy and arduous task in a fraction of the time that it would otherwise take.

Before concluding that a MEDLINE search has neglected a significant portion of the articles published in a particular area, one must be certain that the search was properly constructed and accurately performed. An indispensable tool in using MEDLINE as a time-saving and effective search system is the *Medical Subject Headings* (MeSH), the biomedical thesaurus maintained at the National Library of Medicine and used by its indexers. Created by specialists in thesaurus construction, MeSH stands as one of the great achievements in biomedicine. An analysis of MeSH indicates that appropriate subject headings concerning consultation-liaison psychiatry, such as "mental health services" and "psychiatry" (and their narrower headings) and "referral and consultation," do exist. These would have greatly maximized the authors' search results. Any study that concerns the performance of MEDLINE *must* consider MeSH. Mr. Bareta and associates did not mention MeSH, and their "keywords" are not MeSH headings. This casts serious doubt on the study's conclusions.

It appears to us from this article that the authors are uninformed as well as inexperienced searchers of MEDLINE. While it is certainly reasonable to expect an untrained novice searcher to form an opinion about MEDLINE based on his or her search experience, it is generally not advisable to present this opinion as a valid and comprehensive judgment in a widely read and authoritative medical journal. We hope that future submissions of this nature will receive a thorough and careful review by qualified peers, such as experienced librarian searchers of MEDLINE.

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## Dr. Lyons and Associates Reply

SIR: Mr. Warling and Ms. Gilman clearly agree with us that our computer-assisted search was inadequate. That, however, appears to be the only point on which we agree. We concluded that the failure of the MEDLARS search should serve as a warning to researchers that computer-assisted searches may not be sufficient. Mr. Warling and Ms. Gilman conclude that we are incompetent at computer-assisted searches.

Perhaps a review of the evidence for each perspective would be instructive. We used a trained medical librarian to accomplish our search. From the initial review she took the three keyword phrases that appeared to target best the desired sample of articles, and our computer-assisted review was based on this interactive process. We accept the idea that this might not have been the best of all possible searches, but we feel that it is representative of the standard practice in computer-assisted reviews.

Mr. Warling and Ms. Gilman base their argument about our incompetence on the fact that we did not use MeSH. They then claim that this "would have greatly maximized the authors' search results." They unfortunately provide no data on which to base this claim. If in fact MeSH is "one of the great achievements in biomedicine," it should be a relatively uncomplicated matter to document the claims of its advocates. However, for the purposes of scientific communication, it is problematic to accept these statements as true in the absence of some form of empirical demonstration. We invite Mr. Warling and Ms. Gilman to replicate our study using MeSH. If their results are consistent with their assertions, then they would have a stronger case regarding our skills (or lack thereof).

Should such a replication be undertaken, however, we wish to make two additional points. First, we are not clear what Mr. Warling and Ms. Gilman mean by "greatly maximize." A computer-assisted search should optimize the identification of articles. Thus *all* relevant articles should be identified, but *only* relevant articles should be identified. Both the sensitivity and the specificity of the search are important. Anyone can design a search that would capture all articles (maximum sensitivity). The art exists in accomplishing the task without generating pages of irrelevant titles and abstracts (optimal sensitivity and specificity). Second, we viewed the manual search through specified journals as a "gold standard" by which to evaluate the computer-assisted review. We were not necessarily recommending this as a review strategy, although this form of systematic review has been used with some success (1, 2). We again note that even the manual search was not completely accurate.

We should emphasize that we sincerely hope that Mr. Warling and Ms. Gilman can prove that computer-assisted searches are more effective than we were able to show. Our results, however, were consistent with reports from other fields (3, 4). The development of improved library services through the use of computers is an important priority. We look forward to a day when our technology is that good. We simply are not yet convinced that today is that day.

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## Comments on Psychiatric Aspects of Ulcerative Colitis

SIR: Carol S. North, M.D., and associates (1) urged readers to "forswear unsupported generalizations about the psychiatric aspects of ulcerative colitis." Their conclusion resulted from observing many methodological flaws in the published studies that investigated this question. However, there is more to this story than the limitations of published studies. An analysis of the sociohistorical context in which interest in psychosomatic approaches to ulcerative colitis arose and later declined (2) led to a number of additional conclusions about 1) the difficulty of incorporating psychological factors into biomedical models of disease, 2) the limitations of extending research paradigms appropriate for acute, infectious disease to chronic illness, and 3) the gap between medical and lay understandings of disease.

From the very start, psychosomatic research on ulcerative colitis was methodologically suspect and heavily influenced by larger trends in medicine and psychiatry. A careful review of Murray's original publication (3), which Dr. North and associates and most other reviewers have dutifully cited, demonstrates that two of his four patients had amoebae in their feces; thus, this seminal report does not conform to definitions of ulcerative colitis then or now. It is equally revealing that Murray's research was conducted under George Draper, who had pioneered a psychosomatic approach that emphasized the identification of "constitutional" characteristics which might identify specific types of people who were susceptible to particular illnesses. From the beginning, interest in psychological factors in ulcerative colitis was part of a more general psychosomatic movement in the years between the two world wars.

The most prominent psychosomatic researcher at the time was Franz Alexander. Although caricatured as rigidly adhering to the notion that specific personality conflicts cause specific diseases, Alexander and other researchers were equally interested in studying individual factors that might explain susceptibility to, and exacerbations and remissions of, chronic medical illness. This was and is a legitimate research agenda, which has largely been ignored by modern biomedical scientists. Other factors specific to ulcerative colitis that influenced the rise of interest in psychological factors were its poorly understood pathophysiology, its unpredictable clinical course, and the therapeutic nihilism of practitioners of the time.

Factors that influenced the decline of interest in the psychosomatic hypothesis for ulcerative colitis included the decline of the psychosomatic movement, especially among nonpsychiatrists, and medical advances in the treatment of the disorder. There has also been a "paradigm" shift in our understanding of chronic medical disease: what was formerly labeled psychosomatic is now called immunological. It can be argued that this shift obscures how little progress has been made in our understanding of the role of individual factors in chronic medical diseases.

The sociohistorical approach to ulcerative colitis also focuses our attention on enduring and unresolved epistemological questions involving chronic disease. The repetition of flawed studies of the psychogenesis of ulcerative colitis points to the limitations of conceptualizing the role of psychological factors in chronic disease as analogous to the way specific microbial agents cause acute, infectious disease. The increasing emphasis on such specificity in psychiatric nosology makes it even more difficult to study the role of psychological factors in chronic medical illness. While many persons have noted the need for a biopsychosocial approach, both research and clinical approaches have fallen far short of the rhetoric.

The investigation of psychological factors in ulcerative colitis will undoubtedly be helped by better study design, but it is equally important to correct other mistakes of the past. We need to 1) frame the problem of psychological etiology in a less "either-or" manner (e.g., infectious versus psychogenic), 2) recognize the complex and potentially covarying relationship between emotional and physical symptoms, and 3) investigate the "why me?" and "why now?" questions in chronic disease, which are often the most important ones for patients but are typically outside the medical gaze.

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SIR: The review by Dr. North and associates concluded that the most rigorous studies have failed to find an association between psychiatric disorders and ulcerative colitis. In epidemiological studies, variables associated with both the risk factor and the disease should be considered, as they might have a confounding effect on the presence or absence of an association. Smoking is strongly associated with psychiatric disorders (1) and a decreased risk of ulcerative colitis (2, 3). The net effect of these two combinations could be to mask any association between psychiatric disorders and ulcerative colitis. I wonder whether any of the studies Dr. North reviewed considered smoking status.

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## Dr. North and Associates Reply

SIR: Dr. Hughes is correct that ulcerative colitis is less prevalent in smokers than in nonsmokers. Previous studies have not systematically determined the importance of smoking history when examining relationships of psychiatric illness to the bowel disease. The studies we reviewed did, however, consider all patients who presented clinically with ulcerative colitis. Thus, we still must conclude that in the group that actually expresses this medical illness, psychiatric abnormalities are not more prevalent than they are in the general population. Although a reliable marker (for example, a genetic one) of a predisposition to ulcerative colitis is not presently available, this question could possibly be further explored in future studies.

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## Cigarette Use and Hyponatremia in Schizophrenic Patients

SIR: Michael Allon, M.D., and associates (1) repeated the work of Burn et al. (2) showing that cigarette consumption impairs free water clearance in normal subjects under short-term experimental conditions. They extended that work by showing that the same mechanisms operate under short-term experimental conditions in chronic schizophrenic patients with previous dilutional hyponatremia. Dr. Allon and associates effected a steady-state diuresis with normal free water clearance in six normal subjects and two patients. Then, both groups used cigarettes, which was followed promptly by impaired free water clearance. The authors concluded that cigarette use may contribute to water intoxication among chronic schizophrenic patients.

The authors' first patient presented with a generalized seizure; her plasma and urine osmolalities were 232 and 364 mosmol/kg, respectively. She had a history of polydipsia and eating cigarette butts. The second patient presented with a generalized seizure and had a serum sodium level of 106 mmol/liter and a urine specific gravity of 1.014, equivalent to a urine osmolality of about 520 mosmol/kg (3). He had a history of polydipsia and heavy cigarette smoking.

The authors did not report serial urine osmolalities in their two patients following water intoxication. They suggested that the atypically concentrated urine osmolalities (364 and 520 mosmol/kg) when the patients were water intoxicated were due to the proximity of cigarette use and laboratory measurement. On the basis of the findings in the authors' table 1, the patients must have used cigarettes within 90 minutes of the measurement of urine concentration. More typically, water-intoxicated schizophrenic patients have very dilute urine, and polydipsia and hyposthenuria long antedate the onset of water intoxication (4). We think that the patients of Dr. Allon and associates had the more classic syndrome of inappropriate antidiuresis with mild or no polydipsia and large circulating levels of arginine vasopressin when they were hyponatremic, in contrast to most schizophrenic patients with water intoxication who consume large quantities of water and have low circulating levels of vasopressin when they are hyponatremic (5).

An interpretation that suggests nicotine-induced hyponatremia in these two patients seems weak for four reasons: 1) the patients and the control subjects responded similarly to nicotine challenge, 2) 29% of the U.S. population smokes cigarettes, 3) water intoxication appears almost exclusively among those with advanced and chronic psychosis, and 4) there is no correlation between serum osmolality and serum nicotine levels among schizophrenic patients subject to water intoxication (6). We believe that clinicians will best serve their schizophrenic patients who have dilutional hyponatremia by looking at mechanisms of osmotic regulation that distinguish schizophrenic patients from normal subjects.

Therefore, we recently observed vasopressin secretion in a patient with chronic schizophrenia.

Sampling vasopressin every 10 minutes for 24 hours, we studied one polydipsic, chronically hyponatremic schizophrenic patient and one normal control subject. The number of vasopressin secretory bursts per 24 hours was 26 for the control subject and 24 for the patient. The mean±SD mass of vasopressin secreted per burst was 4.4±1.0 pg/ml for the control subject and 2.0±0.6 for the patient. The mean±SD interburst interval was 53±26 minutes for the control subject and 58±23 for the patient. The mean±SD maximal rate of vasopressin secretion per burst was 0.25±0.05 pg/ml per minute for the control subject and 0.19±0.02 for the patient. The daily vasopressin secretory rate was 216 pg/ml for the control subject and 126 pg/ml for the patient. These highly preliminary observations suggest that the *mass* of vasopressin secreted per burst, but not the number of vasopressin release episodes, was reduced in this patient with schizophrenia and severe water imbalance. Thus, burst mass, not burst frequency, may distinguish schizophrenic patients from normal subjects. Further studies are needed in which additional patients and control subjects are evaluated with various degrees of water intoxication.

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SIR: Dr. Allon and associates presented evidence that excessive smoking might contribute to hyponatremia in schizophrenia. In their article they failed to cite studies that do not support this hypothesis (1), including one study that failed to show that serum nicotine was correlated with plasma or urine osmolality, plasma arginine vasopressin level, or 24-hour urine volume (2). Perhaps Dr. Allon could comment on the discrepancy between their study and these studies.

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## Dr. Allon Replies

SIR: In our study we described two schizophrenic patients who developed severe hyponatremia with inappropriately concentrated urine in the setting of polydipsia and heavy cigarette use. Following their recovery from the hyponatremia, both patients exhibited normal urinary dilution during water loading, which was subsequently impaired acutely by cigarette use. The renal response to smoking during water loading was then shown to be similar to that measured in normal control subjects. We concluded from these observations that by stimulating vasopressin release, cigarette use impaired urinary dilution; in combination with polydipsia, this could produce water intoxication.

Dr. Vieweg and associates and Dr. Hughes believe that our conclusions about the role of cigarette use in the pathogenesis of water intoxication in schizophrenic patients are not warranted. However, neither the similarity of the response to cigarette use in schizophrenic patients and control subjects nor the high prevalence of smoking in the general population militate against our hypothesis. Smoking by itself should not produce water intoxication; there must be concurrent polydipsia. Water intoxication may occur predominantly in patients with advanced psychosis precisely because these patients have the most severe polydipsia. The lack of correlation between serum osmolality and serum nicotine levels in the study by Vieweg et al. (1) does not necessarily exclude a causal relationship. The increase in plasma vasopressin levels after smoking is very short-lived, lasting only 15 minutes (2), whereas the biologic effect on urinary dilution lasts as long as 90 minutes, as our article indicated. Thus, hypo-osmolality may occur after the vasopressin level has returned to normal.

Finally, Dr. Vieweg and associates question the relevance of the short-term experimental conditions in our study. In fact, patients with self-induced water intoxication and psychosis have a normal serum osmolality most of the time, whereas the onset of hyponatremia is acute. We did not intend to negate the importance of acute psychosis in contributing to the development of water intoxication. Perhaps acute psychosis is associated with an exaggeration of both polydipsia and smoking so as to produce acute water intoxication.

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## Test of Dopamine-Blocking Potential of Clomipramine

SIR: Reports by Jeffrey L. Tate, M.D. (1), Roch H. Bouchard, M.D., and colleagues (2), and Thomas M. Brod, M.D. (3) have suggested a potential association between fluoxetine treatment and the development of parkinsonism. Lipinski et al. (4) described akathisia in five fluoxetine-treated patients, indicating a possible antidopaminergic effect of fluoxetine. Baldessarini and Marsh (5) studied both acute and chronic effects of fluoxetine on dopa accumulation in rats and found that the mean reduction in dopa accumulation (corpus striatum, nucleus accumbens, and frontal cortex) was more than 20% in both experimental conditions. All of this clinical and preclinical evidence suggests that serotonin reuptake inhibitors may have neuroleptic-like properties.

In an attempt to test the potential dopamine-blocking action of clomipramine, we decided to count the frequency of blinking in patients with obsessive-compulsive disorder while they were participating in our clomipramine study. Reduced blinking is known to be one of the more sensitive markers for detecting early parkinsonism. The blink counts were made in a quiet examination room at all times of day with the subject in a supine position during the 5-minute resting period before supine blood pressure measurement. The time (in seconds) required for 10 blinks was recorded at baseline (N=12 for weeks 0–2, N=15 for weeks 3–10) and weekly thereafter until the end of the study. The difference in mean±SD number of blinks per minute between baseline (23.8±11.5) and the end of the first week of clomipramine treatment (29.3±9.3) was not statistically significant (t=–1.65, p=0.13). Subsequent weekly blink rates showed no statistically significant difference from baseline. These data suggest that clomipramine does not exert clinically significant antidopaminergic action in patients with obsessive-compulsive disorder.

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## Dr. Bouchard and Associates Reply

SIR: We read with interest the letter of Drs. Kim and Dysken reporting the lack of an antidopaminergic effect of clomipramine. This result may seem to contradict our previous clinical report, since clomipramine and fluoxetine are both considered to be serotonin reuptake inhibitors. However, it must be emphasized that, unlike fluoxetine, clomipramine is not a specific serotonin reuptake inhibitor. The pharmacological actions of clomipramine seem far more complex than those of fluoxetine. In particular, experimental studies suggest that chronic treatment with tricyclic antidepressants results in increased sensitivity of postsynaptic dopamine receptor function in CNS dopaminergic pathways (1, 2). Therefore, an antidopaminergic effect provoked by the enhancement of serotonergic neurotransmission by clomipramine could be counterbalanced by this hypersensitivity of the postsynaptic dopaminergic receptor.

It would be interesting to replicate the study of Drs. Kim and Dysken using fluoxetine.

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## The Homeless Mentally Ill

SIR: In his commentary "Will We Save the Homeless Mentally Ill?" H. Richard Lamb, M.D. (1) followed his rhetorical question "Does society have the right to deny involuntary treatment to this population?" with a number of opinions and recommendations that, taken together, would permit thousands of our homeless but still politically free citizens to live a life dominated by psychiatric control. In his words, "All incompetent and/or dangerous or gravely disabled homeless mentally ill persons should be brought to hospitals, involuntarily if necessary."

In an apparent effort to reassure "some professionals" and perhaps some patients, Dr. Lamb asserted, "*Studies* have shown that, after they have gone into remission, a *large proportion* of patients who had refused treatment state that their involuntary hospitalization was appropriate" (italics added). One of the references he gave (2) was not a study at all. It was a 10-year-old letter to the Editor that referred to some questions its authors asked 20 patients. The other reference (3) was a badly flawed report of a study that lacked control subjects and random selection. A number of involuntary patients were questioned by the staff of the institution in which they were confined at the time. The authors stated, "We are inclined to believe that *at least some of the patients were telling the truth* since it was shown here that a minority freely and explicitly told us that they do not approve of being detained in hospital" (italics added). Upon such thin evidence did Dr. Lamb build his case for setting aside the rights and liberties of so many.

His viewpoint ignores not only the offense to civil liberties in locking up homeless people against their will but also the inherent danger of thus covering up serious political issues about poverty in America. It also denies the obviously coercive aspects of treatment or research when the subjects are deprived of their freedom and civil rights. As students of the mind, we should know that when people are incarcerated against their will, their primary responses will be to the coercive aspects of their experience, thus corrupting any notion of treatment or research (4).

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## Dr. Lamb Replies

SIR: It does not seem productive to get into a prolonged discussion of the merits of the references in my article. Perhaps a more useful approach would be the clinical experience derived from treating schizophrenic patients: they very frequently ask for the opposite of what they want and need; they test for limits until we provide them; they most often respond with relief and lessening or even remission of symptoms when these limits are set; and they can at times, though by no means always, tell us that they felt these limits were helpful. This of course applies to homeless mentally ill persons when they are incompetent to make a decision about treatment and when involuntary treatment is our only alternative.

My article, however, was about much more than involuntary treatment for the homeless mentally ill. One crucial issue has to do with whether we meet the many needs of these unfortunate human beings or whether we place a higher priority on our own needs by adhering to our preconceived ideologies regardless of the plight of the patients. We feel good about ourselves by acting on the basis of what we have already decided is right, but in doing so we do not consider the consequences for the welfare, the safety, the very lives of our patients. Ideology should not determine clinical practice, but rather clinical experience should determine ideology.

The focus of my article was on only that group of the homeless who have chronic and severe mental illness. I believe there is a tendency for some to deny the contribution that severe mental illness makes to homelessness in this particular group. When this happens, a great disservice is done to the homeless mentally ill. We should be mindful of the need for the full range of psychiatric treatment, including assertive case management, supported housing with varying degrees of structure, neuroleptic medications, day treatment, assistance with money management, and a whole array of social and rehabilitative services. The chronically and severely mentally ill, of whom the homeless mentally ill are a subpopulation, must be given the highest priority in public mental health policy if we are to solve their problems and truly give them freedom—the freedom to live the best lives of which they are capable.

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## Avoiding the Charge of Negligent Release

SIR: I enjoyed the article by Norman G. Poythress, Jr., Ph.D. (1) on avoiding negligent release cases and agree that a videotaped exit interview or a "Dangerousness Assessment Sheet" would be helpful in the event of legal proceedings. It is important to note that whichever method is chosen, it must be mandatory for all discharged patients regardless of their perceived dangerousness. Otherwise, if a patient were to prove to be dangerous after having been discharged with the appropriate form or videotape completed, the plaintiff's attorney would surely suggest that the physician in fact deemed the patient dangerous, since the "dangerous patient" protocol was activated.

This clear need to apply the protocol to all patients militates against use of the videotape method, given the extra equipment and physician time that it requires.

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## Dr. Poythress Replies

SIR: Dr. Westreich correctly points out the potential risks and costs of implementing some of the risk management procedures suggested in my article. If a psychiatrist uses such procedures with only some patients, other persons may later infer that the procedures were implemented because the doctor thought the patient might become dangerous. Dr. Westreich's conclusion is that such procedures must therefore be used with all patients and that this makes videotaped exit interviews too costly in terms of physician time.

Let me suggest ways that would allow the selective use of these risk management procedures and yet avoid the undesirable inferences and excessive costs. First, the implementation of these protocols or procedures might be spelled out in policy for only selected classes of patients, and the justification for selective use could be included in the policy. For example, special assessment procedures might be required for all patients admitted after a verdict of not guilty by reason of insanity, because the courts and the public may assume that they are potentially dangerous, whether or not they are viewed clinically as significant risks. In a civil hospital, the procedures might be implemented selectively for patients whose involuntary commitment appears to be based on a finding of dangerousness to others but not for those admitted as gravely disabled, again because of the assumptions that the courts and the public may later make, and not necessarily because the patient is viewed clinically as a risk at the time discharge is considered. While the rationales and policies developed may differ among hospitals, given the different clientele served, an explicit policy directing that these procedures be used selectively with subgroups of patients would probably avoid the undesired inference that might result from the ad hoc use of such procedures.

As for the excessive cost in terms of physician time of videotaped exit interviews, I suggest that any of several members of an interdisciplinary treatment team might conduct the interviews. The team might develop a semistructured interview outline to ensure that certain issues (e.g., attitudes toward medications, current feelings of hostility toward others, intentions to harm others) are discussed with the patient, and the psychiatrist would certainly have to be involved in developing the general interview protocol. Once developed, however, the interview could be conducted by a skilled social worker, nurse, or psychologist, thus minimizing the amount of physician time required.

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## Autonomic Orienting Responses and Criminal Behavior

SIR: In a recent article (1), Adrian Raine, D.Phil., and associates presented their findings on autonomic orienting responses with respect to antisocial behavior. The study itself represents an important contribution toward our understanding of the predisposition to sociopathy. The authors prospectively studied 101 male subjects, first when they were 15 years old and then again at age 24. This was done for the purpose of psychophysiologically comparing those with criminal records (N=17) to the others (N=84). The results demonstrated that smaller measures of certain autonomic orienting reflexes (i.e., skin conductance and deceleratory/acceleratory heart rate) were significantly more prevalent in the subjects with criminal records (31%) than in the control subjects (10%).

These findings may provide us with a better biological perspective of the human reaction of administering physical punishment in response to antisocial activity. This appears to be an innate, even court-mandated reaction in various societies, cultures, and individuals. The punishment can be viewed as a biological adaptation of those living with the criminal, with the purpose of "reorienting" the sociopathic person's nervous system toward more relevant external cues, leading to more socially acceptable behavior. This could represent a form of reconditioning and sensitizing the criminal's autonomic nervous system to correct the perceived conditioned deficits that are observed in antisocial populations (2). It can be questioned whether these punishments correct the perceived deficit or merely stop the outward behavior. Dr. Raine and associates have suggested a better approach, that of using the antisocial person's enhanced "active" attention to motivating stimuli (3) as a means of rehabilitation.

William James, a century ago, wrote that all states of the mind are neurally conditioned. He said that every individual has a different threshold of attention for pain, fear, sensation, misery, etc. and that this threshold will largely determine the individual's philosophy of life (4). He spoke out against the "medical materialists" who judged a person's opinions by their origins and not simply by their own intrinsic value. To the degree that one can separate functional cognition from biological nervous system functioning, it can be argued that antisocial behavior reflects a primary constitutional nervous system outgrowth rather than a primary cognitive defect per se. The cognitive defect can be viewed as secondary to the individual's nervous makeup. It remains to be seen whether this would hold true for other personality types and what the relative contributions of other variables (i.e., psychosocial) to the whole character are.

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## Dr. Raine Replies

SIR: Dr. Mayerhoff raises three important and interesting issues stemming from our article. The first is whether intervention strategies aimed at reversing orienting deficits in antisocial populations should focus on the use of punishments to reorient the individual to relevant socializing cues. A potentially more potent strategy, however, is suggested by recent psychophysiological and behavioral studies (1–3) which indicate that psychopathic individuals are more sensitive than nonpsychopathic individuals to rewards and situations involving "active" attentional processing.

The second issue is whether the autonomic orienting deficits reflect a primary cognitive deficit or whether this cognitive deficit is secondary to a more "hard-wired" biological/genetic deficit. An answer to this question necessarily depends, as Dr. Mayerhoff himself suggests, on the degree to which one can separate functional cognition from the CNS. The fact that autonomic orienting measures and criminality are both in part genetically determined certainly suggests that a hard-wired biological deficit underlies orienting deficits in criminals. In a recent magnetic resonance imaging study (4), we observed that skin conductance orienting is correlated at a level of 0.44–0.60 with area of prefrontal cortex in normal, intact human beings; fewer orienting responses was associated with smaller prefrontal area. Orienting deficits in criminals could therefore be a function of hard-wired prefrontal structural deficits. On the other hand, the fact that antisocial persons appear to be quite capable of allocating their attentional resources when active attention is required (3) could be construed as indicating that passive orienting deficits are more cognitive in nature and that they possess the appropriate "hardware" for attentional processing. Until further experimental evidence is forthcoming, it will be difficult to choose between these two alternatives.

The third issue raised by Dr. Mayerhoff is the extent to which psychosocial variables play a role in mediating criminal behavior. In our study, we measured several important social and cognitive variables (e.g., socioeconomic status, area of residence, academic ability) that have previously been related to crime, but none of these was found capable of mediating the orienting-crime relationships. It is important to emphasize, however, that this does not negate the role of social variables in the development of criminal behavior, nor do these findings negate the possibility of important interactions between social and biological variables in determining crime, since the small sample size precluded a test of this latter possibility. Indeed, we believe that major breakthroughs in the understanding of criminal and psychopathic behavior will depend on the pursuit of these biosocial interactions and the combination of neuroscience research with clinical, social, and cognitive research.

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## Sun Gazing and Photophilia in Schizophrenia

SIR: A letter from Peter S. Kamp, M.D., and associates (1) reported findings similar to ours (2, 3) on sun gazing in psychotic disorders. Interestingly, the first report of this behavior was from Karl Jaspers, describing a schizophrenic patient who gazed at the sun only when psychotic (4). We consider a behavior photophilic when at least one of the following phenomena is present: simple sun gazing, sun gazing secondary to hallucinations or delusions ("sun worship"), and light seeking without sun gazing.

More recently, we presented a report on the first systematic study of sun gazing and other unusual light-related behavior in psychiatric patients (5). We have argued that systematic investigation of light-related behavior helps identify subjects with mild photophilic or photophobic tendencies who otherwise are missed. We found a history of sun gazing in 31% of the patients with schizophrenia when systematic inquiries were made with a specially designed questionnaire (5). The schizophrenic sun gazers had higher photophilia scores (5.1±0.9) and lower photophobia scores (0.9±1.1) than control subjects (photophilia, 3.0±1.0; photophobia, 1.6±1.0) ($p<0.001$). In another study (H. Gerbaldo et al., unpublished data), 10 schizophrenic patients living in an open ward were studied for over 1 year. We observed that four of the 10 patients chose very open, bright areas (about 90,000–100,000 lux) on 50%–70% of the sunny days, showing a clear photophilic light-exposure pattern.

In a recent study, we asked subjects to stop a paced increase in the light intensity of a translucent screen when the light became uncomfortable. The light source was turned off automatically after 15 seconds if the subject had not already stopped it. The thresholds of discomfort at high luminances were found to be higher in the 20 schizophrenic patients (847±232 footcandles) than in the 13 control subjects (387±241 footcandles) ($p<0.001$); the highest thresholds were found in nine schizophrenic sun gazers (944±142 footcandles) and the lowest in one depressed patient (250 footcandles). We hypothesize that decreased sensitivity to light (or an increased threshold of discomfort at high luminances) in schizophrenia probably contributes to the photophilic tendencies (5).

This light-related behavior needs to be studied further for a number of reasons. Sun gazing implies a risk of retinal damage and should not be overlooked (1, 5 . Furthermore, behavioral patterns affecting exposure to light influence measurements of photosensitive neuroendocrine processes. Therefore, systematic evaluation of light-related behavior will complement chronobiological studies of the psychoses (4). Finally, since dopamine has been found to decrease retinal responses to light (6), decreased sensitivity to light and related behavior may reflect a neurophysiological substrate linked to the biology of schizophrenia, thereby offering new research opportunities.

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## What's Wrong With "ECT"?

SIR: When I read the letter from Charles H. Kellner, M.D., and David Ramsey, M.D. (1), my first reaction was to think of a newfangled appellation for ECT. Should it be called artificially induced cerebral dysrhythmia (AICD), or therapeutic cerebral dysrhythmia (TCD), or reversible cerebral dysrhythmia (RCD), or modified Cerletti and Bini procedure (MCBP), or should we use modifications of mythological names such as Zeus and Thor or just call it electroplexy? While looking for other terms, I began to wonder why a new name should not be easily forthcoming when "we know a great deal about how seizures affect the brain, and our knowledge is increasing rapidly" (1).

Although recent years have seen the accumulation of voluminous data concerning ECT, do we really know how ECT works? The most definite aspect of the procedure is that it involves passing a certain amount of electrical current through the brain for a certain duration of time to achieve the therapeutic benefit. Such a procedure can only be designated as electroconvulsive or convulsive therapy until we fathom the underlying mechanism of action.

As Drs. Kellner and Ramsey themselves pointed out, "Knowledgeable people can no longer doubt the safety and efficacy of an electrically induced seizure under general anesthesia for the treatment of severe depression. And few who have firsthand knowledge . . . think it anything other than a modern, humane therapy for a group of very serious illnesses." Surely, then, the answer lies in increasing the number of such knowledgeable people by educating the public and letting them know more about the procedure. We should not be offended by the need to prove yet again that it works.

As I see it, we have two options: 1) changing the existing name and hiding behind the new term or 2) keeping the present name and educating the public about the therapeutic procedure. The first stance is likely to be perceived by the press and the public as defensive. A new name is likely to be as unpopular as were Koch's and Hansen's for tuberculosis and leprosy, respectively. The press is still likely to call it shock therapy or ECT, and the public will wonder what we are defensive about.

Yes, there is a third choice: changing the name and educating the public. However, this has to wait until we can make a change in the existing name that is based firmly on the underlying mechanism of action.

I suggest, too, that there is no need to frighten our patients and their relatives. We should allay their fears by educating them. This education, an integral part of the informed consent process, should (and does) include a description of the procedure, a video demonstration of the procedure for skeptical or fearful patients or relatives, and a discussion about the results. To achieve this there is no need to hide behind novel labels.

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### Dr. Kellner and Dr. Ramsey Reply

SIR: We applaud Dr. Ahuja's creative efforts to coin a new term for ECT and agree with his major premise that the public should be better educated about the procedure. However, we do not believe that a name change need necessarily await the discovery of the underlying mechanism of action of the treatment.

As long as anti-ECT propaganda such as the recent Geraldo Rivera television program continues to misinform the public, we feel that responsible mental health professionals should do everything possible to promote a truthful, balanced view of this life-saving medical procedure. We remain hopeful that changing the name might be a significant part of this effort.

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*Reprints of letters to the Editor are not available.*

THE AMERICAN JOURNAL OF PSYCHIATRY

*Special Articles*

# The Clinical Meaning of Refractory Depression: A Review for the Clinician

Richard Guscott, M.D., and Paul Grof, M.D., Ph.D.

*Objective: The authors' goal is to address the complex issue of treatment-refractory depression from a clinical perspective. Data Collection: They review the literature on the major clinical and methodological issues involved in the treatment and study of treatment-refractory depression as well as primary and tertiary care surveys of patients whose depression has not responded to treatment. Findings: There are methodological problems in defining treatment-refractory depression and in the tertiary care surveys of treatment-refractory depression. The authors define treatment-refractory depression as primarily involving diagnostic-treatment variables rather than patient variables. They articulate these variables as a series of questions the clinician may consider when confronted with patients who are considered refractory: 1) Is the diagnosis correct? 2) Has the patient received adequate treatment? 3) Was a rational stepped-care approach used? 4) How was outcome measured? 5) Is there a coexisting medical or psychiatric disorder that interferes with response to treatment? and 6) Are there factors in the clinical setting that are interfering with treatment? Conclusions: The problem of treatment-refractory depression has to do primarily with the diagnostic-treatment process than with patient variables. This has a number of implications in the areas of training, education, research, and public health. The evidence indicates that improvements in the recognition and treatment of depression are needed.*

(Am J Psychiatry 1991; 148:695–704)

It is generally accepted that a substantial percentage of depressed patients fail to respond to treatment with standard pharmacotherapy. Ayd (1) estimated this percentage to be about 20%. In this paper, we review some of the major clinical and methodological issues involved in the treatment and study of patients with refractory depression. We look first at the issue of defining treatment-refractory depression. Second, we briefly review the tertiary care surveys of patients with the diagnosis of refractory depression. Third, we propose a conceptual schema for understanding the phenomenon of refractory depression and identify both clinical and research issues. Finally, we address some of the broader issues raised by our understanding of the phenomenon of treatment-refractory depression.

## THE PROBLEM OF DEFINITION

The issue of definition poses a major methodological problem in studying treatment-refractory depression, and we found no general consensus regarding this issue. This problem was addressed in 1974 at the World Psychiatric Association symposia on therapy-resistant depression (2, 3). A distinction was made then between absolute and relative treatment resistance—absolute

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was defined as failure to respond to 150 mg/day of imipramine or the equivalent after 4–6 weeks and relative was defined as the failure to respond to less than 150 mg/day. Clearly, by today's standards such a definition would be considered inadequate given the higher doses recommended by most clinicians (4–7). The implication of this early definition was that relative treatment resistance was due to the undertreatment of depression. Since 1974, treatment-refractory depression has been defined according to very "strict" or very "loose" criteria based on the intensity or duration of treatment and the number of treatment modalities applied (8, 9).

The distinction between absolute and relative treatment resistance appears to be crucial for both methodological and obvious clinical reasons. Each likely involves very different variables accounting for the lack of response, including both treatment and patient variables. These variables were well reviewed by Thase and Kupfer (9). Most research has focused on those patients who are relatively unresponsive to treatment, and there is a tendency to equate relative lack of response with nonresponsiveness to tricyclics (10). This is analogous to equating essential hypertension that is unresponsive to thiazide diuretics with refractory hypertension, a terminological confusion that can be avoided by applying a rational stepped-care approach to hypertension (11).

The proposed distinction between relative and absolute failure to respond to treatment begs a number of crucial questions. Does the distinction make clinical sense? Is there truly such a phenomenon as absolute failure to respond? If so, what is the magnitude of this problem? How does it compare to the problem of relative refractoriness with respect to morbidity and mortality?

The evidence from surveys of patients defined as refractory in tertiary care settings points overwhelmingly to undertreatment as the crucial variable in conferring refractoriness on depressed patients (12–15). A majority of the depressed patients referred for tertiary care consultation, including a group referred for psychosurgery, had quite simply not received adequately intensive psychopharmacological treatment.

Consistent with the evidence for the undertreatment of depression, there is evidence that manic-depressive illness is both underrecognized and undertreated. In their recent text, Goodwin and Jamison (16) estimated that no more than one-third of patients with manic-depressive illness receive treatment. This claim is supported by the study of Schou and Weeke (17), who described the undertreatment of patients with affective disorders who committed suicide. Schou and Weeke concluded that a significant percentage of these patients could have benefited from either continuation or prophylactic treatment with antidepressants or lithium.

The findings from tertiary care settings are consistent with the research on the diagnosis and treatment of depression in primary care (18–21). The undertreatment of depression looms as a major problem.

## THE CLINICAL BASIS OF REFRACTORY DEPRESSION

The inescapable conclusion from the research literature on refractory depression and the recognition and treatment of mood disorders generally is that refractory depression is first and foremost a sociological fact—a phenomenon of labeling. That is, patients have refractory depression because they have been labeled as such by their treating clinicians and not necessarily because they do not have the potential to respond to treatment. The evidence clearly points to undertreatment as the primary cause of so-called refractory depression.

Six clinical questions must be answered to understand refractory depression. These are listed in appendix 1. Here we review the best available literature in each area, making specific recommendations with regard to treatment strategies and identifying areas requiring further research.

### *Is the Diagnosis Correct?*

Rather than reviewing the question of the differential diagnosis of depression here, we raise some questions about the differential diagnosis in patients who have been defined clinically as having refractory depression.

The evidence from tertiary care surveys points to the overdiagnosis of primary affective disorders in patients who have been defined as treatment refractory. These patients appear to have had a heterogeneous group of primary disorders. For example, MacEwan and Remick (14) reported that 13.3% of patients defined as treatment refractory had a primary psychiatric disorder other than affective disorder.

The possibility of overdiagnosis of affective disorder is a largely unstudied phenomenon. Whybrow et al. (22) noted that "the availability of relatively specific forms of therapy may . . . have increased the number of diagnoses of affective disorders in recent years. There is evidence that physicians frequently give precedence to a diagnosis for which treatment is available or that holds the promise of a good prognosis." There has been a shift in diagnostic practices toward affective disorders. In many facilities, the diagnosis of affective disorders in general and bipolar illness in particular increased substantially during the past 25 years, probably because of changed therapeutic expectations (23, 24).

This consideration leads directly to the issue of the distinction between primary and secondary depression in patients who are considered refractory. (We are referring to secondary depression in its "derivative" meaning, i.e., as causally derived from a primary nonaffective disorder whether psychiatric or medical.)

It is important to make the distinction between primary and secondary depression for a number of crucial clinical reasons. In the 1984 study by Keller et al. (25) of 97 patients treated at university medical centers, the diagnosis of secondary depression emerged as a major predictor of chronicity of symptoms despite adequate somatic treatment. Two questions remain unanswered from both the tertiary care surveys of treatment-refractory depression and the outcome study of Keller et al.: Was the primary nonaffective disorder identified by the referring clinician? and Was the primary disorder adequately treated? It would appear that the primary nonaffective disorder was not identified, at least in tertiary care surveys, or the patient would not have been referred with the label of treatment-refractory depression.

The drug treatment of secondary depression has been reviewed elsewhere (26). We wish to raise here only the issue of the treatment of the primary nonaffective disorder. We concur with Keller et al. that more intensive somatic treatment of the primary nonaffective disorder might improve the prognosis of the secondary depression.

There is no doubt, however, that the primary-secondary distinction itself is not uncontroversial, as evidenced by its lack of inclusion in *DSM-III-R*. Attempts to validate the primary-secondary distinction by biological measures or treatment response have been largely unsuccessful (27–29).

Clinically, what can we take from these considerations? First, when confronted by a patient defined as having treatment-refractory depression, we must consider the possibility of misdiagnosis—the patient might not have a depressive disorder. Second, we must also consider the possibility that there is a primary nonaffective disorder coexisting with a depressive syndrome. The latter consideration, however, should not preclude somatic treatment of the depression. Rather, it suggests that more careful attention be paid to treatment of the primary disorder.

### *Has the Patient Received Adequate Treatment?*

*Was the dosage adequate?* There is good evidence from both tertiary and primary care surveys that antidepressants are often used in subtherapeutic doses (30). In 1985, Quitkin (30) pointed out that, surprisingly, many research trials of antidepressants use inadequate doses of antidepressants. Even more worrisome are the low doses and inadequate documentation of doses in trials comparing antidepressants with psychotherapy, as reported in 1989 by Meterissian and Bradwejn (31).

Clearly, underdosage is a major problem in both clinical practice and in the research setting. The reasons for underdosage are complex and not fully understood. Underdosage also raises the issue of health care provider compliance. From a practical point of view, however, the issue can be stated quite simply. What dose of a tricyclic antidepressant or monoamine oxidase inhibitor (MAOI) should be used before concluding that the drug is not helpful? Although ideal dose-response studies (i.e., with randomized, homogeneous patient samples and a double-blind design) are few, there is strongly suggestive evidence (32–35) that patients should be treated with 300 mg of imipramine or the equivalent (for tricyclic antidepressants) or 90 mg of phenelzine or the equivalent (for MAOIs) before concluding that the medication is ineffective.

We agree with the emergent consensus on the appropriate doses but recognize that side effects may prevent their attainment, an issue we more fully address later in this paper. The issue of the relationship between response and tricyclic antidepressant levels or platelet MAO inhibition is also more fully addressed later in the paper.

*Was the treatment trial of sufficient duration?* Inadequate length of antidepressant trials emerges as a major factor along with underdosing in the somatic treatment of patients defined as having treatment-refractory depression.

Although there is some evidence that many patients show signs of improvement as early as 3 to 10 days after initiation of treatment with an antidepressant (36, 37), most texts recommend at least 4 weeks of treatment as a minimum trial. However, there is some evidence that 4 weeks is too short a time for an adequate trial with antidepressants. In 1984, Quitkin et al. (38) reanalyzed the data from three studies of the response to antidepressants. In the pooled data, 25% of the patients showed no response at week 4 but did show a good response at week 6.

We can make a number of conclusions on the basis of the current evidence regarding response to antidepressants over time. First, a substantial majority of patients respond during the first 4 weeks of treatment. Second, a substantial minority respond during the first 2 weeks. However, about 25% respond between weeks 4 and 6 if they have received adequate doses of antidepressants.

On the basis of the available evidence we would define an adequate trial of antidepressants as 6 weeks at adequate doses (as previously defined). The first 3 weeks can be used to build up slowly to an adequate dose. Of course, there are many pressures on the clinician to act and switch to other antidepressants when patients fail to respond after 3–4 weeks of treatment. The patient's level of distress, pressure from the family, and even the advice of other mental health professionals can often force the clinician to switch antidepressants prematurely. As clinicians, we should resist such pressures. Clearly, we need to educate the patients, their families, and other mental health professionals about the variable time course of response to antidepressant treatment.

*Was serum monitoring of antidepressants employed, and, if so, how was it used?* We will not review the issue of the relationship between tricyclic antidepressant levels and treatment response. This relationship has been extensively reviewed elsewhere (39–44).

There is reasonable consensus that tricyclic antidepressant serum monitoring is indicated in patients who fail to respond to treatment despite adequate doses and in patients who develop severe side effects at low doses (45, 46). In recent reviews, Preskorn (47, 48) argued strongly for a broader basis for serum monitoring as a means of assessing compliance, maximizing response, avoiding toxicity, minimizing cost, and avoiding medical-legal problems.

The potential of serum monitoring to improve the treatment of depression ought not to be underestimated. However, there is virtually no evidence to demonstrate that the use of serum monitoring in routine clinical practice improves therapeutic outcome. We also suspect that in many clinical situations the monitoring of tricyclic antidepressant levels can lead to inappropriate clinical decisions. We have observed many situations where patients have been kept on subtherapeutic doses because of levels above the "therapeutic" range.

The use of determining platelet MAO inhibition in patients taking phenelzine also requires careful interpretation. Again, there is no research showing that the clinical determination of platelet MAO inhibition in routine clinical practice improves therapeutic outcome. Furthermore, the relationship between platelet MAO inhibition and treatment response is often misinterpreted by clinicians. If we return to the original studies (49, 50), we find that they focused on two groups of patients, one receiving 30 mg of phenelzine and the other receiving 60 mg. There was an association between MAO inhibition and good response in the group receiving the higher dose. This has been erroneously interpreted as meaning that 80% platelet MAO inhibition is sufficient for good treatment. The correct interpretation of the original studies is that 80% inhibition is necessary but not necessarily sufficient for adequate doses. Dose-response studies indicate that 1 mg/kg of body weight of phenelzine may be required in most patients (50).

In summary, although we ought not to underestimate the potential role of laboratory monitoring of antidepressant therapy, we also ought not to overestimate its utility until studies are available on the relationship between its clinical use and therapeutic outcome.

*Were other treatments used?* The evidence from tertiary care surveys is that MAOIs are underused in patients defined as refractory. MacEwan and Remick (14) reported that of those patients defined as refractory and who achieved complete remission with further treatment, 20.3% did so with MAOIs. In addition, Clarry et al. (51) recently reported that only a minority of the psychiatrists they surveyed routinely prescribe MAOIs.

The clinical use of MAOIs has been extensively reviewed elsewhere (50–54). Although the role of MAOIs was originally defined rather narrowly for the so-called atypical depressions, it is clear now that early studies of the use of MAOIs for endogenous depression probably used inadequate doses, which accounted for the poor therapeutic outcome. More recent studies (50, 55, 56) suggested that MAOIs are undoubtedly effective in the treatment of endogenous depression and that there are now broader indications for their use, particularly in the geriatric population. Our own uncontrolled observations and those of others are that MAOIs may be highly efficacious in the treatment of bipolar depression (57). Clearly, further controlled observations are needed.

The indications for ECT in patients with refractory depression have been reviewed by Fink (58). It is clear from the tertiary care surveys that ECT is an underused treatment modality for refractory depression. Although there is good evidence that ECT should be considered a first line in the treatment of psychotic depression, it remains underused even in this disorder (59–62).

It is likely that the attitudes of patients, families, and other clinicians often work against using ECT even when it is strongly indicated. The current climate of negative public opinion about the use of ECT only increases the underuse of this effective treatment in patients who clearly could benefit from it.

It is clear that clinicians in routine clinical practice do not use their full therapeutic armamentarium, a phenomenon worthy of investigation in itself.

*Was compliance a problem?* Noncompliance with antidepressants emerged as a major problem in patients defined as refractory in MacEwan and Remick's study (14). In patients defined as refractory who achieved complete remission of symptoms with further treatment, 8.5% had previously been noncompliant with medication. In the group that was considered only partially responsive after intensive somatic treatment, approximately 17% were noncompliant.

Unfortunately, the major psychiatric texts (63–66) contain little on the issue of compliance. In the 2,000 pages of the fourth edition of the *Comprehensive Textbook of Psychiatry* (64), for example, compliance with medications is mentioned once, and that has to do with compliance with antihypertensives. Goodwin and Jamison (16) noted that of the more than 10,000 articles written about lithium, fewer than 50 dealt substantively with compliance. Given that most psychiatric disorders, and certainly depressive illness, have pronounced effects on cognition and motivation, one would expect the issue of noncompliance to be important for research. However, with few exceptions (67, 68) there is little systematic research in psychiatry in this area. Fortunately, other medical specialties have taken the lead in this area, and there are many randomized trials of strategies for improving compliance (69–71). Psychiatrists have a great deal to learn from this body of research.

The dynamics of noncompliance are complex. Many patients have realistic concerns with regard to side effects. Others are noncompliant for psychological reasons having to do with personality factors, coping style, and beliefs about illness (72). In addition, the prescription of antidepressants occurs in the context of a culture that places a high value on individualism and self-reliance and fears dependency (73). In this context, taking medications is often seen by patients as a crutch. Depression is conceptualized by many patients and their families as not a medical illness for which there is effective treatment but, rather, as a personal failing. This personal failing may be defined by patients in a moral sense, but in our current cultural milieu it is usually defined as a failure of competence as a person.

Although laboratory monitoring may be an invaluable aid to the assessment of noncompliance, nonjudgmental exploration of a patient's difficulties in taking medication as prescribed can be almost as reliable (70). The doses should be scheduled to be convenient and flexibly fitted into the patient's life style. It is also extremely important to explore the patients' and families' conceptual beliefs about the meaning of illness and the role of somatic treatment.

Although risk factors for lithium noncompliance have been proposed, a profile for antidepressant noncompliance has not been established (16). Clearly, further research is warranted.

*Did side effects, real or fictitious, interfere with treatment?* Today, many patients and most clinicians are aware of the potential adverse effects of somatic treatment. However, the attribution of causality of a symptom to a specific drug is not unambiguous, as Sackett et al. (70) pointed out: "The fact that an adverse reaction occurred during administration of a drug provides incomplete evidence that it occurred because of the administration of a drug." Studies have shown that it is very difficult even for clinical pharmacologists to identify with certainty whether a specific symptom or clinical event is due to a drug reaction (68, 69). Koch-Weser et al. (74) demonstrated that the rate of agreement between two clinical pharmacologists assessing whether an adverse drug reaction had occurred was quite low. In another study (75), healthy university students and hospital staff who were not taking any medications were surveyed regarding whether they had experienced any somatic symptoms that are often considered to be side effects of commonly prescribed medications during the previous 72 hours. The investigators, two clinical pharmacologists, found that 81% of the subjects reported having experienced at least one of these symptoms and 7% reported six or more symptoms.

Clearly, the attribution of causality of a symptom to a specific drug can be problematic given the considerable prevalence of somatic symptoms in the general population. "Somatic noise" in a clinical population can make it very difficult to decide if an adverse drug reaction has occurred. In our affective disorders clinic we often see patients who have been referred because of side effects of either lithium or MAOIs who on further investigation clearly did not have side effects of these medications. When rechallenged with either lithium or MAOIs these patients were able to tolerate the medication very well.

As clinicians we must be clear in explaining to patients which side effects we would expect them to tolerate and which side effects would prompt us to change the course of our clinical actions. Nuisance side effects must always be weighed against the consequences of continued illness.

MAOIs deserve special mention because the evidence from tertiary care surveys points to their usefulness in patients who have been defined by their clinicians as refractory (14). We acknowledge that many patients have difficulty tolerating MAOIs due to their hypotensive effects. However, even though these patients are difficult to treat, strategies have been proposed for counteracting this side effect. Cockhill and Remick (76) have written a particularly excellent review of this topic.

### *Was a Rational Stepped-Care Approach Used?*

In other medical subspecialties, a rational stepped-care approach is readily available for the treatment of common medical diseases such as essential hypertension, asthma, and rheumatoid arthritis. Unfortunately, the "rational" stepped-care approach for depression is not as rationally grounded as it might be. Many texts present treatment trees for the use of psychopharmacological agents and decision-making algorithms for which the rational basis is not evident. In addition, many augmenting drugs such as lithium, thyroid supplementation, and L-tryptophan as well as combination regimens are advocated in the literature without delineation of a clear scientific basis for choosing among these various regimens.

In MacEwan and Remick's study (14) 70% of the patients originally defined as refractory who achieved complete remission did so with standard treatment with either a tricyclic antidepressant, an MAOI, or ECT. A small percentage improved with other specific psychopharmacology, including lithium augmentation, combined MAOI-tricyclic therapy, and the use of newer heterocyclic antidepressants. This raises serious questions about the role of the different alternative psychopharmacological treatments advocated because most treatment-refractory patients can improve or even achieve complete remission with standard treatment.

The use of a rational stepped-care approach to depression is clearly important to prevent the unsystematic, casual, and potentially harmful use of various augmenting, potentiating, and combined treatments.

A common recommendation for a stepped-care approach to the treatment of depression is that initially the patient should have two trials of tricyclic antidepressants with different pharmacological profiles followed by a trial of an MAOI followed by a course of ECT (8). Such a recommendation illustrates some of the difficulties in rationally grounding a stepped-care approach for depression.

First, should tricyclic antidepressants always be the first line of treatment? Clearly, there is evidence that in psychotic depression, ECT or combined tricyclic-antipsychotic therapy is the treatment of choice (59, 61, 62, 77, 78). There is also fairly strong evidence that in the so-called atypical depressions, MAOIs should be the first line of treatment (52). Uncontrolled observations suggest that MAOIs may be an efficacious first choice for bipolar depression (57).

The second step in the commonly accepted stepped-care approach is also not without problems. For example, should patients with depression receive a course of two different tricyclic antidepressants before the clinician moves on to the use of ECT or MAOIs? In our view and in the view of others, there is no sound pharmacological rationale for the use of two different tricyclic antidepressants (79). Not only has the attempt to identify biological measures of the differential response to various antidepressants failed but depression is no longer conceptualized as a simple deficiency of one or another neurotransmitter (80).

Further questions can be raised regarding lithium augmentation in view of the popularity of this strategy and its recommendation in the literature as a second step. Although a great deal of optimism was generated by an early report (81), such optimism ought to be tempered by the lack of controlled studies in this area. Mogens Schou (82) has recently reviewed this subject comprehensively.

If we are to have a scientifically grounded second step in the treatment of depression, carefully designed comparative trials of the current psychopharmacological options are desperately needed. For example, patients who fail to respond to tricyclic antidepressants could be randomly assigned to receive lithium augmentation, a second tricyclic antidepressant, or an MAOI. Such a trial would clearly require multicenter collaboration but would help scientifically ground the second step in a rational stepped-care approach to depression.

If the early steps are not satisfactorily grounded, later strategies, including augmenting or combination treatments, are even more problematic. Rationally grounded guidelines are not evident in the literature, however. The reports are often anecdotal, doses of previous medications are seldom given or are subtherapeutic, and trials are often too short by currently accepted standards (83–87). As clinicians and researchers, we should expect standard reporting procedures on the previous treatments of patients who have been defined as refractory in reports that advocate specific pharmacological regimens.

Where does this leave the clinician? We must conclude that a more scientifically grounded stepped-care approach is needed for the treatment of depression. A stepped-care approach would consist of the sequential administration of standard somatic treatments in a systematic and rigorous fashion. We submit that if patients are rigorously diagnosed and systematically treated with standard pharmacotherapy, only a small percentage of patients will require the use of alternative treatments such as combination "cocktails" or various potentiating or augmenting treatments. This is not to deny that they are not necessary for the more refractory patient or that clinicians must not be fully familiar with their rational use.

### *How Was Outcome Measured?*

As in many medical treatments, it is important to specify target symptoms when embarking on a course of treatment for depressive illness. It is also important to differentiate improvement in symptoms from improvement in psychosocial functioning. Studies demonstrate that different types of treatment have effects on different target symptoms. For example, antidepressants have more specific effects on improvement of symptoms but psychotherapy has effects on improvement in psychosocial functioning (88–90).

Although it is important to situate treatment goals within the context of the patient's premorbid level of functioning and mood, caution needs to be exercised in the monitoring of patients with a history of dysthymia before the onset of major depression—patients with so-called double depression (91–93). Evidence indicates that such patients may achieve euthymia with adequate antidepressant treatment (94).

Rating scales are often used in research studies and in the specialized clinic and are very helpful in monitoring recovery (16, 95, 96). In addition, the corroboration of improvement or lack of improvement by family members is indispensable for the ongoing monitoring of treatment.

### *Is There a Coexisting Medical or Psychiatric Disorder That Interferes With Response to Treatment?*

Strongly suggestive evidence points to the coexistence of a medical or nondepressive psychiatric disorder as a problem in depressed patients who are considered refractory to treatment. Akiskal (97) found that unsuccessful recovery in primary depressive disorder was highly associated with chronic medical problems and ongoing alcohol abuse. MacEwan and Remick (14) found high proportions of patients with chronic medical illness or ongoing substance abuse in both a group that was absolutely refractory and a group that was only partially responsive to treatment. These findings are consistent with the findings from studies on rapid cycling bipolar disorder suggesting that undiagnosed medical disease (i.e., hypothyroidism or undiagnosed neurological disease) can be a major factor in the induction of rapid cycling (98, 99).

The important research and basic science question here is whether chronic medical illness or ongoing substance abuse affects the capacity of the brain to respond to pharmacological treatment. As of yet, we know little about these phenomena.

At a clinical level, when faced with a patient who is not responsive to systematically administered standard treatment, it is useful to consider an undiagnosed or inadequately treated medical problem and ongoing substance abuse as a contributor to nonresponse.

### *Are There Factors in the Clinical Setting That Are Interfering With Treatment?*

The undertreatment of depression occurs in a clinical setting that is the context through which the various clinical variables discussed here operate. There is good evidence that the setting determines a major part of the variance in the treatment that depressed patients receive. In 1986, Keller et al. (100) found that the choice of somatic therapy or psychotherapy for depressed patients was related not to patient variables but to the characteristics of the center in which the patients received treatment. Certain treatment centers were more likely to use intensive somatic therapy and others were more likely to use intensive psychotherapy. The type of psychotherapy offered varied by center; some offered psychotherapy proper and others offered medication-oriented psychotherapy. In attempting to identify the variables responsible for the differences among centers, Keller et al. concluded that the major determinants were the beliefs and prescribing practices of the centers' clinicians.

That there are widespread differences among psychiatrists in how they conceptualize depressive illness is clear to even the most junior resident. The same constellation of symptoms and behavior can be described from a psychological, sociological, or biological perspective. It should be pointed out that the relationship between our conceptual models and both clinical behavior and therapeutic outcome is a largely unstudied phenomenon. Although most psychiatrists today would not support rigid adherence to any one particular conceptual model, the multifactorial approach is not always an improvement. The multifactorial or biopsychosocial approach can be considered an improvement only if future research demonstrates that it results in an improvement in both our clinical behavior and our patients' therapeutic outcomes. One of the problems with the multifactorial approach is the difficulty created for treatment planning when etiological priority is not established, as Bridges (15) has discussed eloquently.

In addition, more research is needed on the effects that refractory patients have on clinicians and the results for treatment and diagnostic practices. In our view, depressed patients who fail to respond to treatment have very predictable effects on clinicians at behavioral, affective, and cognitive levels. The patient's failure to respond to treatment often results in feelings of impotence in the clinician, leading to frustration, feelings of incompetence, and a lowering of self-esteem. The direct result of this is often anger. This chain of feelings produced in the clinician by the patient's failure to respond has complex effects. Behaviorally, it results in avoidance of the patient. At the affective level, it results in feelings of dysphoria, anger, and decreased tolerance for the patient's expression of distress. Perhaps the most serious consequence of this chain of feelings is the effects at the cognitive level. According to our own uncontrolled observations, patients who do not respond to treatment might be given an additional axis II diagnosis. The cause of the depression might be attributed to personality features of the patient or marital or family problems. The patient might be given a diagnosis of dysthymia or characterological depression. The role of consultation in breaking this chain of emotional reactions cannot be overemphasized.

## DISCUSSION

Our review of the literature suggests that the vast majority of cases of refractory depression are due to variables involving the diagnostic and treatment process rather than the patient. Although there can be little doubt that there is a group of depressed patients who are clearly more treatment resistant than others and might be absolutely refractory, the vast majority of these patients are only relatively refractory. As of yet, we know little about the absolutely refractory subgroup.

The underrecognition and undertreatment of depression at all levels of care is a major public health problem and represents a substantial burden of morbidity, mortality, and economic loss. There is even more reason for concern when one considers the possibility that the prevalence of depression may be increasing in the population born since World War II (101, 102).

Paradoxically, the widespread underrecognition and undertreatment of depression exist at a time when our knowledge of the psychobiology of depression is increasing dramatically and when there is definitive evidence concerning the value of somatic treatment. We can take small comfort in the recognition that these problems are not specific to psychiatry but are shared by our colleagues in other medical specialties. One has only to consider the widespread underdiagnosis and undertreatment of asthma at a time when the morbidity and mortality from asthma are increasing worldwide (103–106). This occurs at a time when our understanding of the pathophysiology of asthma has advanced greatly and efficacious treatment with minimal side effects is available (105).

Our conclusions have a number of implications in the areas of training, education, research, and public health. The low intensity of somatic treatment found in both primary care and tertiary care settings raises serious questions about the psychopharmacology knowledge base of physicians and the training that psychiatrists receive in psychopharmacology. Most residency programs in Canada do not yet have formal training programs in psychopharmacology. The situation is similar in the United States and has prompted the American College of Neuropsychopharmacology to propose a model psychopharmacology curriculum for psychiatric residents (107). The position of the college is worth serious consideration by psychiatric educators in Canada. The model curriculum proposed does not restrict itself to training in the knowledge of drugs and their side effects but recognizes the importance of the psychotherapeutic and social-psychological dimensions of psychopharmacological treatment. This cannot be overemphasized as crucial to the training of residents in the prescribing of somatic treatments. The proper prescription of somatic treatment involves complex psychotherapeutic and assessment skills that are not often taught in conjunction with training in somatic therapies in Canadian residency programs. In most postgraduate programs in psychiatry, the psychotherapies, whether individual or family, are taught as completely separable skills from those which are involved in using biological treatments. Consequently, many clinicians do not recognize the psychotherapeutic dimension of somatic treatment. Training in psychopharmacology should also include training in the psychotherapeutic aspects of somatic treatment.

From a research perspective, two areas clearly require further investigation. First, serious questions need to be raised about the clinician's conceptual understanding of depression as a medical illness and the various attitudinal, affective, and cognitive factors that account for the wide differences in treatment across clinical settings. If, as Keller et al. (100) suggested, it is factors in the setting that account for differences in treatment, we must admit we know little about the variables in the diagnostic-treatment process that determine clinical behavior and therapeutic outcome. Second, as mentioned, future research studies are needed to develop a rationally grounded stepped-care approach to depression. This ought to include the investigation of the early steps in the treatment of depression, particularly the issue of lithium augmentation versus alternative treatments, and strategies for patients who are absolutely refractory.

From a public health perspective, strategies are urgently needed to improve the recognition and treatment of depression at all levels of care. Two recent initiatives are worthy of mention here: the Depression Recognition and Awareness Program of the National Institute of Mental Health in the United States (108) and the program of the Swedish Committee for the Prevention and Treatment of Depression (109). Unfortunately, there is no Canadian counterpart to such initiatives.

## CONCLUSIONS

In this paper we have reviewed the clinical issues involved in understanding treatment-refractory depression. After addressing the issue of definition, we have attempted to define treatment-refractory depression as primarily involving diagnostic-treatment variables rather than patient variables. We articulated these variables as a series of questions the clinician may consider when confronted with patients as refractory.

The evidence indicates that improvement in the recognition and treatment of depression is needed. Given our advances in knowledge of the psychobiology of depression and the availability of safe, efficacious treatment, it is a therapeutic tragedy that depression appears to be so poorly treated.

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## APPENDIX 1. Clinical Questions for Understanding Refractory Depression

1. Is the diagnosis correct?
2. Has the patient received adequate treatment?
    a. Was the dosage adequate?
    b. Was the treatment trial of sufficient duration?
    c. Was serum monitoring of antidepressants employed and, if so, how was it used?
    d. Were other treatments used?
    e. Was compliance a problem?
    f. Did side effects, real or fictitious, interfere with treatment?
3. Was a rational stepped-care approach used?
4. How was outcome measured?
5. Is there a coexisting medical or psychiatric disorder that interferes with response to treatment?
6. Are there factors in the clinical setting that are interfering with treatment?

# The Serotonin Syndrome

Harvey Sternbach, M.D.

*Objective and Method: A review of the literature on the serotonin syndrome in animals and human beings was conducted, and 12 reports of 38 cases in human patients were then analyzed to determine the most frequently reported clinical features and drug interactions, as well as the incidence, treatment, and outcome of this syndrome. Findings: The serotonin syndrome is most commonly the result of the interaction between serotonergic agents and monoamine oxidase inhibitors. The most frequent clinical features are changes in mental status, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, and tremor. The presumed pathophysiological mechanism involves brainstem and spinal cord activation of the 1A form of serotonin (5-hydroxytryptamine, or 5-HT) receptor. The incidence of the syndrome is not known. Both sexes have been affected, and patients' ages have ranged from 20 to 68 years. Discontinuation of the suspected serotonergic agent and institution of supportive measures are the primary treatment, although 5-HT receptor antagonists may also play a role. Once treatment is instituted, the syndrome typically resolves within 24 hours, but confusion can last for days, and death has been reported. Conclusions: The serotonin syndrome is a toxic condition requiring heightened clinical awareness for prevention, recognition, and prompt treatment. Further work is needed to establish the diagnostic criteria, incidence, and predisposing factors, to identify the role of 5-HT antagonists in treatment, and to differentiate the syndrome from neuroleptic malignant syndrome.*

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Serotonin (5-hydroxytryptamine, or 5-HT), discovered by Rapport et al. (1) in 1948, has been shown to have a major role in multiple psychiatric and nonpsychiatric states (anxiety, depression, aggression, pain, sleep, appetite, migraine, and emesis) (2). Two serotonergic agents, fluoxetine and clomipramine, have been on the market in the United States since 1988, and it is expected that others (sertraline, fluvoxamine) will follow in this decade.

Increasingly since the 1960s, a condition of serotonergic hyperstimulation called the "serotonin syndrome" has been described in animals and human beings. This article reviews the history, clinical manifestations, proposed pathophysiology, incidence, precipitating factors, treatment, and outcome of this syndrome with the purpose of helping clinicians to prevent, recognize, and treat the syndrome in their practice.

## HISTORY

CNS effects of the 5-HT precursor L-tryptophan (L-Trp) in human beings were reported by Smith and Prockop (3) in the early 1960s. These investigators studied L-Trp in seven normal subjects and found euphoria, drowsiness, and sustained nystagmus in all of the subjects at the two highest doses, 70 and 90 mg/kg. Other signs included hyperreflexia, unsustained ankle clonus, and clumsiness with tandem walking. Neurological disturbances associated with high L-Trp intake were similarly reported in rhesus monkeys (4). Oates and Sjoerdsma (5) administered single doses of L-Trp, 20–50 mg/kg, to seven hypertensive patients being treated with the monoamine oxidase inhibitor (MAOI) β-phenylisopropylhydrazine. The symptoms and signs they noted included feeling drunk and dizzy, as well as clonus, restlessness, hyperactive reflexes, and diaphoresis in the absence of any significant change in blood pressure or heart rate, with symptoms abating within 24 hours. Since it had been shown in animals (6, 7) that administration of L-Trp increased brain levels of tryptamine and 5-HT, Oates and Sjoerdsma concluded that the signs and symptoms they had noted were due to elevated concentrations of tryptamine and 5-HT in their subjects. In a follow-up study, Hodge et al. (8) gave five hypertensive subjects a decarboxylase inhibitor before treating them with pargyline or isocarboxazid, preventing the formation of tryptamine and 5-HT and thus blocking the nystagmus, jaw tremor, hyperreflexia, clonus, sweating, and intoxication that L-Trp produces.

After the late 1950s, there were reports on the use of

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**TABLE 1. Summary of 12 Clinical Reports of the Serotonin Syndrome in 38 Patients**

| Authors | Diagnosis | Age (years) | Sex | Medications[a] | Time to Onset |
|---|---|---|---|---|---|
| Baloh et al. (17) | Bipolar disorder, depressed | 26 | F | Tranylcypromine, 20 mg; L-Trp, 2 g | 1 hour |
| Insel et al. (18) | Obsessive-compulsive disorder | 35 | F | Clomipramine, 100 mg, 4 weeks after clorgyline was stopped | 30 minutes |
|  | Obsessive-compulsive disorder | 30 | M | Same as above | "Immediately" |
| Thomas & Rubin (19) | Depression | 21 | M | Phenelzine, 90 mg; L-Trp, 6 g | 2 hours |
| Pope et al. (20) | Depression alone (N=1) or with eating disorder (N=8) | 20–42 | All F | Tranylcypromine, 40–130 mg, and L-Trp, 1–6 g (N=8); phenelzine, 75 mg; L-Trp, 13 g; lithium; benzodiazepine | 2 days to 4 weeks from first dose of L-Trp |
| Levy et al. (21) | Depression | 57 | M | Phenelzine, 60 mg; L-Trp, 2 g | 3 hours |
|  | Bipolar disorder, depressed | 28 | M | Phenelzine, 105 mg; lithium (0.9 meq/liter); L-Trp, 2 g | 2 hours |
|  | Depression | 31 | F | Phenelzine, 90 mg; L-Trp, 2 g | 2 hours |
| Guze & Baxter (22) | Bipolar disorder, depressed | 30 | F | Lithium, 1500 mg; isocarboxazid, 50 mg; alprazolam, 6 mg; levothyroxine, 0.15 mg; L-Trp, 8 g; carbidopa, 75 mg | 2 days |
| Price et al. (23) | Depression | 63 | M | Tranylcypromine, 30 mg; lithium, 900 mg; L-Trp, 2 g | 1 week |
| Steiner & Fontaine (24) | Obsessive-compulsive disorder (N=5) | 34–58 | 3 M, 2 F | Fluoxetine, 50–100 mg; L-Trp, 1–4 g/day for 7–22 days | "Rapidly" to a few days |
| Sandyk (25) | Parkinson's disease | 68 | M | Bromocriptine, 20 mg; L-dopa/carbidopa, 25/250 mg t.i.d. | 7 days |
| Sternbach (26) | Depression | 31 | F | Tranylcypromine, 20 mg, 6 days after fluoxetine, 20 mg, was stopped | 2–3 hours |
| Kline et al. (27) | Depression | 45 | F | Fluoxetine, 40 mg; levothyroxine; propranolol; quinidine; hydroxyzine; followed by thioridazine, 50 mg; L-Trp, 500 mg; tranylcypromine, 50 mg | 2½ hours after L-Trp and thioridazine were added |
| Feighner et al. (28) | Unipolar (N=9) and bipolar (N=3) depression | 22–50 | 10 F, 2 M | Fluoxetine, 10–100 mg; phenelzine, 30–60 mg (N=9), or tranylcypromine, 10–140 mg (N=4). All but one took other psychotropics, including L-Trp (N=2), benzodiazepines (N=10), neuroleptics (N=6), lithium (N=1), anticonvulsants (N=2), stimulants (N=2), antidepressants (N=5) | Not specified |

[a] L-Trp=L-tryptophan.

L-Trp to potentiate the effects of MAOIs in depression (9–13). In one such study (13), patients were given 12–18 g/day of L-Trp with 60 mg of phenelzine; no hypertensive reactions were noted, although one patient who ingested 18–20 g all at once was found to have increased deep tendon reflexes, muscle twitching, and clonus of the masseter, all of which subsided within 12 hours. Further, tricyclic antidepressants were also combined with MAOIs, and Beaumont (14) reported on interactions between these two classes of drugs that were manifested by sweating, restlessness, muscular twitching, rigidity, hyperpyrexia, and loss of consciousness and that led to death in several patients. In all instances, the patients were already taking MAOIs (mebanazine, tranylcypromine) when the tricyclic was added. Subsequently, White and Simpson (15) reviewed the literature on combined MAOI-tricyclic treatment, noting that the adverse reactions to most MAOI-tricyclic combinations in cases in which there was not an overdose differed from typical hypertensive crises, as there was rarely marked elevation of blood pressure, headache, or a cerebrovascular accident. The more typical picture was that of an agitated delirium with generalized hypertonicity, seizures, hyperpyrexia, and variable elevations of heart and respiratory rate, which often progressed to coma, a pattern considered to be "nonspecific."

During the same period of time, there were separate reports in the literature on animals about a behavioral syndrome seen when serotonergic stimulation was induced by the combined use of L-Trp or 5-HT reuptake inhibitors and MAOIs or by stimulation of 5-HT receptors with 5-HT agonists such as 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeODMT) or 8-hydroxy-2-(di-*N*-propylamino)tetralin (8-OH-DPAT). In 1980 Gerson and Baldessarini (16) reviewed this serotonin syndrome

**TABLE 1 (continued)**

| Clinical Features | Treatment | Time to Resolution |
|---|---|---|
| Myoclonus, drowsiness, ocular oscillations, ataxia | Not specified | 24 hours |
| Restlessness, leg contractions, diaphoresis, myoclonus, hyperreflexia, clonus, blood pressure 170/90 mm Hg, temperature 37.4 °C | Clomipramine discontinued | 24 hours |
| "Upper motor neuron" symptoms, myoclonus, "cardiac irritability" | Same as above | 6 hours |
| Shivering, diaphoresis, jocularity, fearfulness, ocular oscillations, hyperreflexia, dysmetria, ataxia | Both drugs stopped | 24 hours |
| Confusion, disorientation, myoclonus, agitation, hypomania | L-Trp and MAOI stopped | 12 hours to 4 days |
| Myoclonus, ataxia, tremor, diaphoresis, hyperreflexia, feeling drunk | L-Trp stopped | 12 hours |
| Myoclonus, hyperreflexia, diaphoresis, teeth chattering, jaw quivering | L-Trp and phenelzine stopped | 12 hours |
| Restlessness, hyperreflexia, diaphoresis, teeth chattering | L-Trp stopped | 8 hours |
| Tremors, myoclonus, hyperreflexia, ataxia, nystagmus | Propranolol, 20 mg every 3 hours | Not specified |
| Diaphoresis, hyperventilation, shivering, hyperreflexia, increased muscle tone, temperature 38.5 °C | L-Trp stopped | Not specified |
| Agitation, nausea, diarrhea, paresthesia, chills, headache, cramps, incoordination, aggressive behavior, worsening obsessive-compulsive disorder, poor concentration | L-Trp stopped | "A few weeks" |
| Shivering, myoclonus, tremor, hyperreflexia, clonus, diaphoresis, diarrhea, temperature 37.9 °C, blood pressure 180/100 mm Hg | Methysergide, 2 mg b.i.d. | 12 hours after third dose |
| Shivering, double vision, nausea, confusion, anxiety, teeth chattering | Tranylcypromine stopped | 24 hours |
| Headache, insomnia, muscle contractions, ataxia, restlessness, neck pain, diaphoresis, flushing, tremor, rigidity, hyperreflexia, seizures, hypotension, disseminated intravascular coagulation | All drugs stopped; dantrolene, dopamine, *l*-ephedrine, lidocaine | 44 hours (death) |
| Tremor, agitation, confusion, hypomania, myoclonus, diarrhea, diastolic pressure 90–120 mm Hg | Not specified | Not specified |

in animals and noted that the characteristic features were tremor, rigidity, hypertonicity, hind-limb abduction, Straub (rigidly arched) tail, lateral head shaking, treading movements of the forelimbs, hyperreactivity to auditory stimuli, myoclonus, generalized seizures, and variable autonomic responses including salivation, penile erection and ejaculation. Since 1982 there have been 12 reports (17–28) in the literature on human beings about 38 patients who were given various combinations of serotonergic agents that resulted in the serotonin syndrome (table 1), with the notable exception of the case reported by Sandyk (25), in which the presumed cause of the serotonin syndrome was a combination of bromocriptine with L-dopa/carbidopa (further discussed in the section Drug Interactions).

A review of the signs and symptoms in all 38 reported cases (table 2) reveals mental status changes (confusion, hypomania) as the most frequent, followed by restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, and incoordination. The frequencies reported, however, are likely to be artifactually low, as some authors did not report or assess all possible signs and symptoms. It is probable, in retrospect, that the toxic interactions reported by Beaumont (14) and White and Simpson (15) also reflected the serotonin syndrome.

## PATHOPHYSIOLOGY

The preponderance of evidence that the constellation of signs and symptoms labeled as the serotonin syndrome is, in fact, due to 5-HT comes from animal models. The literature on human beings in which 5-HT is implicated in the serotonin syndrome is primarily

**TABLE 2. The Most Common Clinical Features of the Serotonin Syndrome in 38 Patients in 12 Reports**

| Clinical Feature | N | % |
|---|---|---|
| Mental status changes | | |
| Confusion | 16 | 42 |
| Hypomania | 8 | 21 |
| Restlessness | 17 | 45 |
| Myoclonus | 13 | 34 |
| Hyperreflexia | 11 | 29 |
| Diaphoresis | 10 | 26 |
| Shivering | 10 | 26 |
| Tremor | 10 | 26 |
| Diarrhea | 6 | 16 |
| Incoordination | 5 | 13 |

anecdotal, with the exception of the reports by Oates and Sjoerdsma (5) and Hodge et al. (8).

Gerson and Baldessarini (16), in their review of the serotonin syndrome in animals, noted that treatments inducing this syndrome include L-Trp or 5-HT reuptake inhibitors given with MAOIs and stimulation of 5-HT receptors with agonists such as 5-MeODMT or 8-OH-DPAT. The serotonin syndrome can be blocked by pretreatment with *p*-chlorophenylalanine, an inhibitor of 5-HT synthesis, and by 5-HT receptor antagonists such as methysergide. There has been debate about the role of catecholamines in the serotonin syndrome, since L-dopa and MAOIs in combination produced a behavioral syndrome similar to that seen with L-Trp and MAOIs (29), which was nevertheless blocked by methysergide (30).

The identification of different types of 5-HT receptors (31–33) in the past decade has led to speculation that the 5-$HT_{1A}$ receptor is involved in the serotonin syndrome. Lucki et al. (34) compared the ability of the 5-$HT_2$ receptor antagonists ketanserin and pipamperone to block the serotonin syndrome in rats with that of two nonselective 5-HT antagonists, methysergide and metergoline. They noted that only the nonselective antagonists were able to block the serotonin syndrome, while the 5-$HT_2$ antagonists blocked only the head-shake response. Further, Goodwin et al. (35) reported that the serotonin syndrome in rats is mediated by the postsynaptic 5-$HT_{1A}$ receptor, a finding confirmed in mice by Yamada et al. (36). There are, however, some discrepancies in the literature about the ability of 5-$HT_2$ receptor antagonists to block the serotonin syndrome, and, as noted by Smith and Peroutka (37), some of these discrepancies are probably due to the different methods used for rating the syndrome and the different drugs administered to induce it, as well as the choice of specific behavioral signs to be rated. The literature nevertheless indicates that 5-$HT_{1A}$ receptor activation is responsible, in large part, for the serotonin syndrome (35–38).

Anatomically, serotonergic cell bodies are primarily found in brainstem nuclei, particularly the dorsal and median raphe (39), which give rise to most of the ascending serotonergic projections. The more caudal brainstem raphe nuclei give rise to intrinsic brainstem connections and some projections to the spinal cord. As discussed by Lucki et al. (34), the 5-HT receptors responsible for producing the serotonin syndrome are located in the lower brainstem or spinal cord and are most likely 5-$HT_1$ receptors.

Graham and Ilett (40) discussed the importance of both 5-HT and dopamine in the development of the serotonin syndrome when MAOIs are combined with non-MAOIs. In particular, they suggested that the ratio of the concentration of the non-MAOI antidepressant required to halve 5-HT uptake in synaptosomal preparations ($IC_{50}$) to the $IC_{50}$ for dopamine uptake could be related to the incidence of side effects in combined therapy. Agents with low ratios, clomipramine and fluoxetine, were highly likely to cause serious reactions. Amitriptyline and imipramine were intermediate, and trimipramine had a very low potential for producing a serotonin syndrome.

Blier et al. (41) reviewed the effects of tricyclics, MAOIs, 5-HT reuptake inhibitor antidepressants, ECT, and 5-$HT_{1A}$ receptor agonists on 5-$HT_{1A}$ receptors, both presynaptically and postsynaptically, as well as on overall 5-HT neurotransmission. All of these treatments, and lithium as well, have in common the enhancement of 5-HT neurotransmission, albeit through different modifications of the 5-$HT_{1A}$ autoreceptors and postsynaptic receptors. Given these findings, one means of assessing the role of 5-HT in the serotonin syndrome would be to measure directly the concentration of brain 5-HT. Using intracranial dialysis as a means of measuring extracellular levels of 5-HT in vivo, Sleight et al. (42) assessed the relation between extracellular 5-HT and behavior following administration of selective and nonselective MAOIs and L-Trp. Although they were able to raise extracellular 5-HT levels with clorgyline, for example, they were not able to induce the serotonin syndrome. Inhibition of both MAO-A and MAO-B was considered to be essential for the development of the serotonin syndrome, but increased extracellular 5-HT appears not necessarily to result in the syndrome. Sleight et al. postulated that the syndrome may also be the result of a change in the extracellular level of some other, not defined, compound.

In summary, evidence points to the importance of 5-$HT_{1A}$ activation or modification in brainstem and spinal cord neurons, with enhancement of overall 5-HT neurotransmission, as a necessary but possibly not sufficient cause of the serotonin syndrome. Since this hypothesis is based on the literature on animals, however, caution must be used when extrapolating these findings to human beings, as has previously been discussed (15).

## INCIDENCE

The incidence of the serotonin syndrome in human beings is unknown. Prospective studies have not been conducted, and the syndrome is likely to be underreported because it is not recognized, it is confused with neuroleptic malignant syndrome, or it appears in different gradations (mild, moderate, or severe). The cases reviewed by Beaumont (14) and White and Simpson (15), for example, probably represented the serotonin syndrome, as did reports of interactions between meperidine and isoniazid or iproniazid (43, 44). Further, there have been reports of cases in which the serotonin syndrome was thought to be neuroleptic malignant syndrome (27, 45), since there is much overlap between the signs and symptoms of the two. Rosebush and Stewart (46), for example, noted in their prospective study of neuroleptic malignant syndrome that the most frequent clinical features were fever, tachycardia, delirium, diaphoresis, rigidity, muteness, tremulousness, and movement disorder. Thus, Kline et al. (27) initially believed that their patient had neuroleptic malignant syndrome but later changed the diagnosis to serotonin syndrome; Brennan et al. (45) reported that a patient had neuroleptic malignant syndrome "without neuroleptics" while taking a combination of phenelzine, lithium, L-Trp, diazepam, and triazolam.

The incidence of the serotonin syndrome secondary to L-Trp will decline now that all products which contain L-Trp have been removed from the U.S. market because of the association of L-Trp with the eosinophilia-myalgia syndrome (47). However, L-Trp could be put back on the market if it is determined that contaminants were responsible for the cases of eosinophilia-myalgia syndrome, and clinicians should remain alert to this possibility.

The serotonin syndrome has been reported in patients with unipolar and bipolar depression, obsessive-compulsive disorder, eating disorders with depression, and Parkinson's disease. Except for the last disorder, the concentration of cases in these diagnostic groups is probably an artifact of prescribing these types of agents for patients with these conditions. The early literature on the same interactions in patients with tuberculosis given meperidine with isoniazid or iproniazid (43, 44) suggests, however, that anyone could develop this syndrome when given the "wrong" combination of serotonergic agents. Further, there are not, at present, adequate data to suggest that sex or age plays an important role in the incidence of or predisposition to this syndrome. A prospective study is needed to assess accurately the incidence of the serotonin syndrome. Additionally, to facilitate recognition and reporting, consensus is needed to establish formal diagnostic criteria, possibly including different gradations such as mild (tremor, confusion, incoordination), moderate (agitation, hyperreflexia, diaphoresis, shivering), and severe (fever, myoclonus, diarrhea). Suggested diagnostic criteria are listed in appendix 1.

## DRUG INTERACTIONS

The drug interactions most commonly reported in connection with the serotonin syndrome are those between L-Trp and MAOIs, with or without concomitant lithium (table 3). In the cases in which lithium was also prescribed and its levels were reported (21–23), the levels were within normal limits. Further, it has been shown that in animals lithium enhances the serotonin syndrome produced by either 5-MeODMT (48) or 8-OH-DPAT (49), suggesting that lithium may also enhance this syndrome in human beings when it is administered with serotonergic agents.

**TABLE 3. The Most Common Drug Interactions Associated With the Serotonin Syndrome in 38 Patients in 12 Reports**

| Drug Combination[a] | Number of Patients | Reference Numbers for Reports |
|---|---|---|
| L-Trp and an MAOI (with lithium) | 16 | 17, 19, 20–23, 27 |
| Fluoxetine and an MAOI | 14 | 26–28 |
| Fluoxetine and L-Trp | 5 | 24 |
| Clomipramine and clorgyline | 2 | 18 |
| Bromocriptine and L-dopa/ carbidopa | 1 | 25 |

[a] L-Trp=L-tryptophan; MAOI=monoamine oxidase inhibitor.

Fluoxetine in conjunction with MAOIs (26–28) or L-Trp (24) is the second most frequent drug combination associated with the serotonin syndrome. Marley and Wozniak (50) reported that in rats the most intense serotonin syndromes with MAOIs have been those seen with the 5-HT reuptake inhibitors, and they cautioned against the sequential use of these agents (fluoxetine, clomipramine, citalopram, paroxetine) with MAOIs. Additionally, since the serotonin syndrome has been reported when MAOIs were used after fluoxetine had been discontinued (26–28), the manufacturers of fluoxetine notified physicians on June 28, 1988, of three fatalities possibly secondary to use of tranylcypromine after withdrawal of fluoxetine. They recommended that at least 5 weeks elapse between discontinuation of fluoxetine and initiation of an MAOI.

Combinations of MAOIs with tricyclic antidepressants were not formally connected with the serotonin syndrome until the report of Insel et al. (18). In both of their patients, the syndrome developed when clomipramine was started 4 weeks after discontinuation of the MAO-A inhibitor clorgyline. As noted by Insel et al. (18), MAO-A may have a delayed recovery time following irreversible inhibition, with approximately 20% reduction in enzyme activity remaining at 4 weeks, and "adaptive changes" that could contribute to a drug interaction may also persist. Further, in a comparison of tranylcypromine with the reversible MAO-A inhibitor brofaromine, Bieck and Antonin (51) reported that 30 days were needed for complete normalization of the pressor response to tyramine after discontinuation of tranylcypromine, suggesting that tyramine could still interact adversely with the irreversible MAOIs at 4 weeks, which is consistent with the report of Insel et al. (18). Both reports suggest, therefore, that caution must also be used when serotonergic agents are started within 2–4 weeks of discontinuing an MAOI.

Sandyk (25) reported a case of serotonin syndrome in a patient with Parkinson's disease who had been hospitalized for reevaluation of his antiparkinsonian treatment. He had been taking bromocriptine, 60 mg/day, for nearly 3 years. Bromocriptine was reduced to 20 mg/day, and L-dopa/carbidopa was started, with the dose raised during 1 week from one to three 25/250-mg tablets a day. On the seventh day of this regimen, a "toxic encephalopathic syndrome" developed, which was manifested by shivering, myoclonus, hyperreflexia, clonus, tremor, diaphoresis, anxiety, diarrhea, a temperature of 37.9 °C, blood pressure of 180/100 mm Hg, and tachycardia. Sandyk reviewed evidence that L-dopa becomes decarboxylated to dopamine in serotonergic neurons, which could then cause displacement of intraneuronal 5-HT stores into the synaptic cleft and onto 5-HT receptor sites. Dickinson and Curzon (52) reported, however, that the dopamine agonist apomorphine inhibited the serotonin syndrome. Because Sandyk's patient (25) responded to treatment with the 5-HT antagonist methysergide, an agent reported to induce akathisia (53), it is likely that his patient did have a serotonin syndrome and not a misidentified neuroleptic malignant syndrome secondary to reduction of a dopamine agonist (bromocriptine), a condition which would probably have worsened with a dopamine antagonist.

Buspirone, a 5-$HT_{1A}$ partial agonist with weak dopaminergic activity (54), has not been reported to produce the serotonin syndrome in human beings, although when Neppe (55) used high doses of buspirone (up to 160 mg/day) to treat tardive dyskinesia in a woman with bipolar disorder who was taking lithium, she developed diarrhea at doses above 60 mg/day. The literature on animals, however, has been variable on this subject. Two reports showed full (56) or partial (37) serotonin syndromes secondary to buspirone, while another (57) did not. Gepirone, a related compound, was shown to induce the serotonin syndrome in rats (57).

Fenfluramine acts as both a 5-HT releasing agent (58) and a 5-HT reuptake inhibitor (59) and has been shown to induce the serotonin syndrome in rats (58, 60). Hollander et al. (61) reported on the adjunctive use of fenfluramine with either fluoxetine, fluvoxamine, or clomipramine for the treatment of obsessive-compulsive disorder, although no evidence of the serotonin syndrome was apparent in patients taking these combinations.

Two reviews in journals of anesthesia (43, 44) noted that the MAOI-meperidine (pethidine) interaction is one of central serotonergic overactivity. These reviews discussed patients experiencing muscle twitching, fever, hyperreflexia, diaphoresis, hypotension, hypertension, coma, and death. Meperidine has been reported (62) to block the neuronal reuptake of 5-HT and, in conjunction with an MAOI, to cause an increase in the 5-HT content of the CNS. Similarly, dextromethorphan blocks neuronal uptake of 5-HT and has been implicated in the serotonin syndrome (63) when used with an MAOI. Further, Hansen et al. (64) recently reported an interaction in a patient who was given 100 mg of pentazocine in conjunction with 40 mg of fluoxetine. Within 30 minutes of taking this combination, the patient complained of lightheadedness, anxiety, nausea, and upper extremity paresthesias, in addition to which he was diaphoretic, flushed, ataxic, tremulous, and hypertensive. Hansen et al. speculated that their patient's reaction was secondary to serotonergic excitation.

## TREATMENT

No prospective studies evaluating the treatment of the serotonin syndrome in human beings have been conducted. Treatment strategies, therefore, are based on case reports of human patients and the literature on animal models of the syndrome.

The published reports since 1982 indicate that in human patients, if the added offending agent (e.g., L-Trp) is discontinued, the syndrome will often resolve on its own within 24 hours. Supportive measures can be used, however. These include cooling blankets for hyperthermia, intramuscular chlorpromazine as an antipyretic and sedative agent, artificial ventilation for respiratory insufficiency, anticonvulsants for seizures, clonazepam for myoclonus, and nifedipine for hypertension (15, 28, 43, 44).

Animal models have suggested that pretreatment with agents that deplete 5-HT or block 5-HT receptors will prevent the serotonin syndrome (16, 34, 36, 50, 65). More specifically, however, the blockade of 5-$HT_1$ receptors is crucial, since 5-$HT_2$ antagonists did not block the syndrome (34). Sandyk (25) successfully treated the serotonin syndrome by using the nonspecific 5-HT antagonist methysergide. Cyproheptadine, another nonspecific 5-HT receptor antagonist, has also blocked the syndrome in animal models (16), although there are no reports in the literature on its use in this syndrome in human beings.

It has been reported that β blockers block 5-HT receptors (30, 66) and inhibit the serotonin syndrome induced by L-Trp and tranylcypromine (30). Further, it has been noted that propranolol is a 5-$HT_{1A}$ receptor antagonist (54, 67). Guze and Baxter (22) were able to use propranolol to block the serotonin syndrome in a patient taking isocarboxazid, L-Trp, and lithium. It should be noted, however, that in the one report of a fatality (27), the patient appeared to have already been taking propranolol as part of an ongoing medication regimen and still developed the serotonin syndrome.

The literature suggests that the optimal treatment approach is to discontinue the suspected medication, provide supportive measures when necessary, and wait for the syndrome to resolve. In cases in which these measures are not effective, however, methysergide and propranolol can be considered as adjuncts to treatment. Further research is needed, however, to delineate the role of these agents in the treatment of the serotonin syndrome in human beings.

## OUTCOME

The measurement of outcome prior to the first published report that recognized the serotonin syndrome in human beings (17) is fraught with difficulty because of cases of overdose with MAOIs and tricyclics. In the 12 reports since 1982 on the 38 patients with the serotonin syndrome (17–28), one fatality was recorded (27); the syndrome resolved in all of the other cases once the offending agent that had been added was discontinued. Further, resolution typically occurred within 24 hours, although when delirium was present, it took up to 4 days to abate. There were only two reports (22, 25) that specific treatment, propranolol or methysergide, was instituted and found to be effective.

The one fatality in this series (27) was a complicated case in which a patient taking multiple medications (fluoxetine, levothyroxine, propranolol, quinidine, and hydroxyzine) was hospitalized for severe depression. Fluoxetine was discontinued, and 10 hours later the patient was started on 20 mg of tranylcypromine, followed the next day by 50 mg of thioridazine (for agitation and depersonalization), 30 mg of tranylcypromine, and 500 mg of L-Trp for insomnia. Within 2½ hours of receiving L-Trp, she experienced muscle contractions and headache, followed by restlessness, neck pain, fever, diaphoresis, tremulousness, rigidity, and hyperreflexia. Since it was presumed, initially, that the patient had neuroleptic malignant syndrome, dantrolene and bromocriptine were administered, but she went on to have a seizure, require intubation, and develop ventricular tachycardia and hypotension. Oral and nasal bleeding were noted, and her temperature rose to 42.2 °C. Laboratory evaluation showed elevated creatine kinase levels, and results of coagulation studies were consistent with disseminated intravascular coagulation. The patient died approximately 49 hours after the onset of symptoms; the autopsy listed the cause of death as neuroleptic malignant syndrome, although the authors opined, in retrospect, that this patient had the serotonin syndrome instead, noting that the rapid onset of symptoms (within 3 hours) after thioridazine, a low-potency neuroleptic, was unusual for neuroleptic malignant syndrome. (This was, apparently, one of the first deaths reported to the manufacturer of fluoxetine as possibly being linked to a fluoxetine-tranylcypromine interaction.)

Brennan et al. (45) reported on a fatal outcome in a 42-year-old woman with depression who had been treated daily with phenelzine, 45 mg; lithium, 800 mg; L-Trp, 1 g; diazepam, 6 mg; and triazolam, 0.25 mg. She came to the emergency room because of restlessness, sweating, and confusion. Within 3 hours she developed coma, with hypertonicity, hyperreflexia, fever (42.5 °C), tachycardia, hypotension, a serum creatine kinase level of 41,355 U/liter (normal range=24–175 U/liter), and progression to disseminated intravascular coagulation after 12 hours. Since she was presumed to have neuroleptic malignant syndrome, dantrolene was administered, and her temperature returned to normal within 14 hours. In spite of supportive care, antibiotics, mechanical ventilation, and peritoneal dialysis for acute renal failure, severe hepatocellular damage ensued, and the patient died on the sixth day. This patient probably had a serotonin syndrome, rather than neuroleptic malignant syndrome, and her course of illness was very similar to that of the patient of Kline et al. (27).

In summary, the serotonin syndrome typically appears to be a self-limited condition that resolves quickly when offending agents are removed, although fatalities can occur, which makes early recognition and treatment vital.

## CONCLUSIONS

The serotonin syndrome is a toxic hyperserotonergic state, typically the result of combining serotonergic agents with MAOIs, that results from hyperstimulation of brainstem and spinal cord 5-HT$_{1A}$ receptors. This syndrome usually resolves with discontinuation of the suspected serotonergic agent or agents and conservative supportive measures. In severe cases, 5-HT receptor antagonists may be helpful, although their exact role in treatment has yet to be elucidated. The incidence of the syndrome is not known but could rise because of the introduction of more specific serotonergic agents into clinical practice. Heightened awareness by clinicians will help to minimize prescription of combinations of medications that have a higher probability of inducing the syndrome, and if it develops, this same awareness should lead to prompt institution of measures to resolve it.

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## APPENDIX 1. Suggested Diagnostic Criteria for Serotonin Syndrome

A. Coincident with the addition of or increase in a known serotonergic agent to an established medication regimen, at least three of the following clinical features are present:
   1) mental status changes (confusion, hypomania)
   2) agitation
   3) myoclonus
   4) hyperreflexia
   5) diaphoresis
   6) shivering
   7) tremor
   8) diarrhea
   9) incoordination
   10) fever
B. Other etiologies (e.g., infectious, metabolic, substance abuse or withdrawal) have been ruled out.
C. A neuroleptic had not been started or increased in dosage prior to the onset of the signs and symptoms listed above.

# Benzodiazepines in the Treatment of Schizophrenia: A Review and Reappraisal

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Objective: *Benzodiazepines, either alone or added to neuroleptics, have been studied extensively as treatments for schizophrenia, but no consensus regarding their efficacy has been reached. The authors review the double-blind trials in the literature and relate the findings to the neurobiology of benzodiazepine actions.* Method: *The clinical review included all double-blind studies through 1989 that could be identified by means of* Index Medicus *and computer-assisted searches and by the cross-referencing of articles. The findings from the 14 studies of benzodiazepines used alone and the 16 studies of adjunctive therapy are presented separately.* Results: *The studies reviewed suggest that 1) response is highly variable, and about one-third to one-half of patients improve; 2) benzodiazepines are potentially most useful as adjuncts to neuroleptics in the acute management of psychotic agitation, although actual antipsychotic effects have also been observed in some patients; 3) relatively higher doses of benzodiazepines may be associated with better response; and 4) therapeutic effects, when seen, develop rapidly but diminish after several weeks in some patients. The authors explore the neurobiological bases of benzodiazepine action, which presumably underlie their efficacy in schizophrenia and may help explain the variability of response.* Conclusions: *Future research on benzodiazepines in the treatment of schizophrenia should focus on features that predict response, the relation of dopamine or other neurotransmitter systems to therapeutic effects, the schizophrenic symptoms most amenable to benzodiazepine treatment, changes in neuroleptic dose during benzodiazepine augmentation, the role of benzodiazepines in maintenance therapy, and the optimal characteristics of benzodiazepine treatment.*
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Benzodiazepines, either used alone or added to neuroleptics, have been studied extensively as treatments for schizophrenia (1–36); the first double-blind study was reported in 1961 (21). Despite the large number of studies conducted since that time, no consensus regarding their efficacy has been reached (2–7). Indeed, the clinical literature on this topic has become unwieldy and difficult to interpret because of the widely varying methods, diagnostic criteria, and statistical analyses used, the large number of unblinded anecdotal cases reported, and the highly divergent results obtained. Despite this lack of clarity in the literature, clinicians are increasingly relying on adjunctive benzodiazepines in the therapy of treatment-resistant schizophrenic patients (37, 38).

The purpose of this article is twofold: 1) to review the double-blind trials in the clinical literature on the use of benzodiazepines for schizophrenia and to synthesize the major findings and 2) to integrate these findings with our understanding of the neurobiology of benzodiazepine actions. In our clinical review we included all double-blind studies through the end of 1989 that could be identified by means of *Index Medicus* and computer-assisted searches and by the cross-referencing of articles. We report separately studies that used benzodiazepines as solitary treatments and studies that used them as adjuncts to neuroleptics.

## REVIEW OF THE LITERATURE

### *Benzodiazepines as Sole Agents*

Benzodiazepines used in the treatment of schizophrenia, along with their relative potencies, are listed in table 1. The results of the double-blind trials of

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benzodiazepines used as sole agents in the treatment of schizophrenia (8–21) are summarized in table 2. Nine of the 14 studies (8–11, 13, 16, 17, 20, 21) indicated that benzodiazepines have some positive effects, although in nearly all 14 studies some individual patients responded well and others poorly. One difficulty in interpreting this literature is that several of the studies, particularly the early ones, had significant methodologic limitations, e.g., heterogeneous patient groups, nonstandardized diagnostic systems and global rating instruments, and inadequate statistical analyses. All of the studies reported after 1975 showed positive effects (8–11), although one examined only the acute (1–24 hours) effects of benzodiazepines (11) and one examined only the prolongation of remission (10).

Among the reviewed studies, assessment of behavioral improvement was based on different variables, e.g., reductions in anxiety and agitation, global impairment, and psychotic symptoms specifically. Of the 10 studies examining psychotic symptoms (8–13, 15–18), six (8–11, 16, 17) indicated favorable effects on these symptoms and one of the remaining four (13) showed benzodiazepines to be superior to placebo but inferior to neuroleptics. There is a suggestion, therefore, that benzodiazepines by themselves may have some, even pronounced, antipsychotic efficacy for some patients.

### *Benzodiazepines as Adjunctive Agents*

The results of the double-blind studies of benzodiazepines used as adjuncts to neuroleptics (12, 22–36) are summarized in table 3. Seven of the 16 studies showed positive effects (23, 26, 28–30, 32, 33), and four indicated mixed or only transiently positive effects (12, 22, 24, 25). As was the case with the investigations examining benzodiazepines as solitary treatments, in nearly all of these studies some individual patients responded well and some responded poorly to benzodiazepine augmentation. Nearly two-thirds of the studies reported in 1975 or later showed positive results (22, 23, 26, 28–30, 32), and, of the 13 studies in which psychotic symptoms were specifically examined, five showed positive effects on such symptoms (23, 28, 29, 32, 33) and two showed mixed or transiently positive effects (12, 22). Positive effects, when seen, ranged from "mild" (e.g., less than 10% reduction in symptoms) (29) to "moderate," "marked," or "striking" (23, 26, 28, 32). A variety of systems for diagnosing schizophrenia were used in the studies of benzodiazepines as both solitary and adjunctive treatments (tables 2 and 3). No association between response and diagnostic system was apparent in the reports that cited the criteria used. However, 19 of the 30 reports did not include the diagnostic criteria used.

Our review of the literature on the use of solitary and adjunctive benzodiazepines highlights both the variability of findings among studies and the variability of clinical response within studies. In the following sections, we extract certain themes from the review of the literature and attempt to identify various sources of variability in clinical response.

**TABLE 1. Relative Potencies of Benzodiazepines Studied in the Treatment of Schizophrenia[a]**

| Benzodiazepine | Mean Dose (mg/day)[b] | Relative Potency in Inhibiting Specific [$^3$H]Diazepam Binding to Rat Brain Cortex Membrane (compared to unlabeled diazepam) |
|---|---|---|
| Diazepam | 22 | 1.00 |
| Chlordiazepoxide | 58 | 0.29[c] |
| Alprazolam | 2 | 1.97[d] |
| Lorazepam | 5 | 3.17[d] |
| Clonazepam | 1–5 | 4.20[c] |
| Estazolam[c] | 1.5 | 0.90[d] |
| Camazepam[c] | 40 | 0.006[d] |

[a] Only the benzodiazepines studied in the double-blind trials reviewed in this article (8–36) are included in this table. Inclusion here does not imply effectiveness or superiority in the treatment of schizophrenia.

[b] For all drugs except clonazepam, the number shown is the mean of the recommended dose range for the treatment of anxiety (in nonschizophrenic populations). Clonazepam is not listed for this indication, and the numbers shown are the range of doses used in the studies (25, 27).

[c] Data adapted from Möhler and Okada (39).

[d] Data adapted from Shibuya et al. (40).

## FACTORS IN CLINICAL RESPONSE

### *Solitary Versus Adjunctive Treatment*

Several studies have suggested that benzodiazepines are superior to placebo in the treatment of schizophrenia, whereas fewer have suggested equivalence or superiority to neuroleptics. Therefore, when effective, benzodiazepines are probably best used as adjunctive treatments for treatment-resistant patients (1, 4, 5, 28, 32, 41) or as solitary treatments for patients unable to tolerate neuroleptics.

### *Comparisons of Specific Drugs*

There is no clear evidence that specific benzodiazepines differ in their efficacy in treating schizophrenia. Among the studies of benzodiazepines as solitary agents, positive results were shown in 67% of those using diazepam (8–11, 16, 17) and 43% of those using chlordiazepoxide (13, 20, 21) (Fisher exact probability=0.67, n.s.). The studies of benzodiazepines used as adjunctive treatments suggested more favorable results with high- or intermediate-potency benzodiazepines (23, 26, 28–30, 33), but this finding is confounded by the higher doses (corrected for potency) used in those studies and other studies contradict this generalization (25, 27). It has been tentatively suggested that triazolobenzodiazepines may be mildly superior to typical benzodiazepines (5), at least in the short-term treatment of negative symptoms (24). Such differences in

**TABLE 2. Double-Blind Studies of Benzodiazepines Used Alone to Treat Schizophrenia**

| | Subjects | | |
|---|---|---|---|
| Authors | N | Diagnosis | Drug Treatment |
| Jimerson et al., 1982 (8) | 6 | Schizophrenia (N=5), schizoaffective disorder (N=1) (RDC) | Placebo for at least 2 weeks, then diazepam added as tolerated up to 300 mg/day for 1–2 weeks |
| Nestoros et al., 1982 (9) | 12 | Paranoid schizophrenia (RDC) | Diazepam (N=6, 70–400 mg/day) or placebo (N=6) for 7 days, then haloperidol (30 mg/day) added for 6 weeks |
| Nishikawa et al., 1982 (10) | 43 | Remitted schizophrenia with history of several relapses[a] | Diazepam (N=13, 15 mg/day), chlorpromazine (N=10, 75 mg/day), haloperidol (N=10, 3 mg/day), or placebo (N=10) |
| Lerner et al., 1979 (11) | 40 | Acute schizophrenia or schizoaffective disorder[a] | Single dose of haloperidol (N=20, 20–35 mg i.v.) or diazepam (N=20, 30–40 mg i.v.) |
| Holden et al., 1968 (12) | 22 | Chronic schizophrenia, active psychosis[a] | Chlordiazepoxide (60–100 mg/day) and placebo for 8 weeks each |
| Hekimian and Friedhoff, 1967 (13) | 30 | Acute and chronic schizophrenia[a] | Placebo (N=10), chlorpromazine (N=10, <450 mg/day), or chlordiazepoxide (N=10, <230 mg/day) for 30 days |
| Gundlach et al., 1966 (14) | 39 | Schizophrenia with moderate to severe anxiety[a] | Diazepam (N=20, 15–40 mg/day) or placebo (N=19) for 6 weeks |
| Stonehill et al., 1966 (15) | 20 | Chronic psychosis: schizophrenia (N=18, two patients had had prefrontal lobotomies), paranoid state (N=1), or postencephalitic psychosis (N=1) | Chlordiazepoxide (75–150 mg/day), diazepam (30–60 mg/day), and two new benzodiazepines (LAXIV, LAXVII) for 4 weeks, each with 2 weeks of no medication between periods |
| Maculans, 1964 (16) | 37 | Schizophrenia (N=36) or alcoholic organic brain syndrome (N=1), all refractory to neuroleptics[a] | Chlorpromazine (200–600 mg/day), chlorprothixine (200–600 mg/day), and diazepam (20–60 mg/day) for 3 weeks each with 1-week placebo washout between treatments |
| Rao, 1964 (17) | 62 | Schizophrenia[a] | Diazepam (N=32, 30–60 mg/day) or placebo (N=30) for 6 weeks |
| Merlis et al., 1962 (18) | 80 | Schizophrenia or "other psychosis"[a] | Individualized doses for 4 weeks, approximately as follows: chlorpromazine (N=20, 150 mg/day), diazepam (N=20, 30 mg/day), chlordiazepoxide (N=20, 75 mg/day), or placebo (N=20) |
| Azima et al., 1962 (19) | 34 | Schizophrenia or psychotic depression, all with anxiety[a] | Chlordiazepoxide (N=17, 20–200 mg/day) or placebo (N=17) for 5 days to 3 weeks[d] |
| Hankoff et al., 1962 (20) | 110 | Schizophrenia or other disorder[a] | Chlorpromazine (N=17, ≥150 mg/day), chlordiazepoxide (N=21, ≥30 mg/day), or placebo (N=72) for 2 weeks[e] |
| Smith, 1961 (21) | 41 | "Mainly schizophrenia"; a few cases of manic-depression[a] | Chlorpromazine (N=13, 150–700 mg/day), chlordiazepoxide (N=13, 150–700 mg/day), or placebo (N=15) for 14 weeks |

[a] Diagnostic criteria not cited.
[b] Patients and one psychiatric rater were blind, but the second psychiatric rater was not.
[c] Each medication in "double-blind" study always had the same code letter.
[d] Chlordiazepoxide group: schizophrenia, N=8; depression, N=9. Placebo group: schizophrenia, N=14; depression, N=3.
[e] Chlorpromazine group: schizophrenia, N=10; other disorders, N=7. Chlordiazepoxide group: schizophrenia, N=16; other disorders, N=5. Placebo group: schizophrenia, N=46; other disorders, N=26.

efficacy are possible, since triazolobenzodiazepines have a somewhat different spectrum of biochemical, electrophysiological (42, 43), and behavioral (44, 45) effects. Further clinical trials directly comparing high-potency benzodiazepines are required to address this issue.

### *Onset and Duration of Response*

The onset of a benzodiazepine's therapeutic action may be remarkably rapid. Various authors have noted beneficial effects of orally administered benzodiazepines within the first day to several days or weeks of treatment (4, 9, 11, 12, 13, 23–25, 33, 35, 46–49), before neuroleptics typically reach maximum efficacy. Despite this early onset of activity, however, several studies suggest an early termination of the therapeutic effect, frequently around the 4th week of treatment (4, 12, 13, 24, 25, 34, 35). These findings raise the possibility of tolerance to the therapeutic effects of benzodiazepines. More long-lasting benefits have been shown by other studies (10, 17, 21, 23, 33), however, and by anecdotal evidence regarding individual patients (24, 46, 50, 51).

**TABLE 2 (continued)**

| Design | Results |
|---|---|
| Crossover | Of three patients tolerating diazepam doses of 250–300 mg/day, two showed "modest" to "marked" improvement (decreased impulsivity, hostility, and delusions and increased spontaneity and sociability), the third showed little change but a dramatic worsening upon withdrawal; two showed no change or worsening; the most responsive patients had responded previously to neuroleptics |
| Between groups | Of six patients taking diazepam, five improved; positive and negative symptoms improved rapidly |
| Between groups; 50% relapse time | Diazepam had a better 50% relapse time than placebo (88 versus 16 days; haloperidol=74 days, chlorpromazine=165 days); neuroleptics superior to diazepam at 3 years |
| Between groups | At 4 hours diazepam showed somewhat better improvement in BPRS total score, global clinical inventory, and hostility-suspiciousness. At 24 hours haloperidol showed somewhat better improvement in global clinical inventory and hostility-suspiciousness, but the two drugs were equal in lowering BPRS total, thought disorder, and activation scores |
| Crossover | Chlordiazepoxide not superior to placebo |
| Between groups$^b$ | All treatments resulted in clinical improvement, but chlorpromazine was superior to chlordiazepoxide, which was slightly superior to placebo; four chlordiazepoxide patients showed good responses, generally with higher doses |
| Between groups | No significant difference in global anxiety, "slight increase" in paranoia; however, even in anxious nonschizophrenic patients, diazepam was not superior in relieving anxiety |
| Crossover | No significant changes in total target symptom ratings with any compound, although some patients became "better" with chlordiazepoxide and LAXVII and "worse" with diazepam and LAXIV |
| Crossover | "Fair" to "good" responses in 59.5% of patients with diazepam, 46.0% with chlorpromazine, and 52.7% with chlorprothixine; diazepam was superior for anxiety, depression, apathy, withdrawal, confusion, and somatization and was equivalent for hallucinations, delusions, ideas of reference, and poor self-care |
| Between groups | Improvement in 63% of patients taking diazepam and 20% of those taking placebo; improvement in anxiety, hallucinations, depersonalization, and delusions |
| Between groups$^c$ | No differences between any agent and placebo; authors commented on a "loosening of research control" |
| Between groups | No significant effect on subjective or observer-rated anxiety; psychotic symptoms not evaluated |
| Between groups | Chlordiazepoxide was significantly superior to placebo and was equivalent to chlorpromazine on global improvement ratings and subjective adjective checklist; results with schizophrenic patients were not reported separately |
| Between groups | Chlordiazepoxide was superior to chlorpromazine and placebo on clinical global ratings, but no statistical analyses were reported |

### *Relationship of Response to Dose and Plasma Level*

The authors of several prior review articles (3, 5, 52) have noted that higher doses of benzodiazepines appear to be associated with more favorable response. In our review of studies using benzodiazepines as solitary treatments, the mean±SD doses (in diazepam equivalents per day) in the studies with the positive and negative results were 124.1±103.4 and 32.8±6.4 mg, respectively (Wilcoxon ranked sum test: $W=21.0$, $p<0.05$). In the studies using benzodiazepines as adjunctive treatments, the mean dose was 54.1±34.5 mg in the positive studies and 22.0±21.4 mg in the negative studies (Wilcoxon ranked sum test: $W=21.5$, $p<0.05$). Such data suggest a dose-response relationship but are not conclusive, since few studies have internally assessed dose-response relationships.

A significant association between plasma benzodiazepine level and clinical response has been shown in some studies (24, 25) but not in others (23). Pharmacokinetic interactions between benzodiazepines and concomitantly administered neuroleptics are likely to be either clinically insignificant (47) or absent (23). It should be noted that tolerance (reduction in intrinsic

**TABLE 3. Double-Blind Studies of Benzodiazepines Added to Neuroleptics to Treat Schizophrenia**

| | Subjects | | |
|---|---|---|---|
| Authors | N | Diagnosis | Drug Treatment |
| Pato et al., 1989 (22) | 17[a] | Chronic schizophrenia (*DSM-III* and RDC) | Alprazolam (≤5 mg/day) or placebo added to stable fluphenazine regimen for 4–6 weeks |
| | 4 | Schizophrenia (*DSM-III* and RDC), outpatients | Either lorazepam (N=2, 0.75 mg/day to highest dose tolerated) or alprazolam (N=2, 0.5 mg/day to highest dose tolerated) added to stable neuroleptic regimen |
| Wolkowitz et al., 1988 (23) | 12 | Schizophrenia (*DSM-III* and RDC), inpatients | Alprazolam (mean=2.87 mg/day) added to fluphenazine (mean=26.4 mg/day) for 4–6 weeks |
| Csernansky et al., 1988 (24) | 55 | Schizophrenia (RDC), outpatients selected to have at least mild negative symptoms | Alprazolam (N=18, mean dose=3.7 mg/day), diazepam (N=20, mean dose=39 mg/day), or placebo (N=17) added to neuroleptics for up to 6 weeks |
| Altamura et al., 1987 (25) | 24 | Schizophrenia, disorganized (*DSM-III*), in acute exacerbation | Haloperidol (3–19 mg/day) plus clonazepam (N=12, 3 mg/day) or placebo (N=12) |
| Nestoros et al., 1983 (26) | 10 | Treatment-resistant schizophrenia (RDC) | After 2-week placebo period, diazepam (35–200 mg/day) added to stable neuroleptic regimen for 12 weeks |
| Karson et al., 1982 (27) | 9 | Chronic schizophrenia (RDC), inpatients | After 2-week placebo period, neuroleptic regimen stabilized for 2 weeks—haloperidol (20–60 mg/day), mesoridazone (600 mg/day), or fluphenazine (40–80 mg/day)—then clonazepam (initially 1 mg/day and adjusted to optimum dose) added for 28 days |
| Lingjaerde, 1982 (28) | 51 | Auditory hallucinations with poor response to neuroleptics (schizophrenia, N=46; manic-depression, N=2; reactive psychosis, N=3) (*ICD*-8) | Three successive 3-week periods of estazolam (6 mg/day), placebo-estazolam, or placebo-estazolam-placebo; 47 patients were concomitantly receiving neuroleptics |
| Lingjaerde et al., 1979 (29) | 23 | Chronic schizophrenia (N=19), reactive paranoid psychosis (N=3), or epileptic psychosis (N=1),[b] not fully responsive to neuroleptics | Diazepam (15 mg/day) and placebo added to stabilized neuroleptic regimen for 3 weeks each |
| Marneros, 1979 (30) | 20 | Schizophrenia with prominent affective symptoms (K. Schneider) | Camazepam (N=10, 40 mg/day) or placebo (N=10) added to haloperidol for 3 weeks |
| Ruskin et al., 1979 (31) | 8 | Chronic schizophrenia with positive and negative symptoms,[b] unresponsive to neuroleptics | Diazepam (40 mg/day for 1 week, then 80 mg/day for 2 weeks) and placebo added to haloperidol (15 mg/day) |
| Kellner et al., 1975 (32) | 6 | Schizophrenia (*DSM-II*) with prominent anxiety not relieved by increasing doses of neuroleptics; only patients who responded to open-label chlordiazepoxide (300 mg/day) and relapsed while taking placebo were included[c] | Chlordiazepoxide (150–300 mg/day) or placebo added to stable regimen of trifluoperazine (N=1, 15 mg/day) or thioridazine (N=5, 200–800 mg/day); each treatment lasted 1–2 weeks |
| Guz et al., 1972 (33) | 60 | Schizophrenia (N=49), dementia (N=3), manic-depression (N=3), paranoia (N=2), epileptic psychosis (N=1), phobic neurosis (N=1), and stimulant dependence (N=1)[b] | Haloperidol (3 mg/day) plus lorazepam (N=30, 6 mg/day) or placebo (N=30); doses adjusted clinically; treatment periods were 4 weeks each |
| Hanlon et al., 1970 (34) | 140 | Acutely ill, newly admitted patients "in need of phenothiazines" not including patients with "regression-nonreactivity"[b] | Fluphenazine (6–20 mg/day) plus chlordiazepoxide (N=71, 40 mg/day) or placebo (N=69) for 32 days |
| Hanlon et al., 1969 (35) | 112 | Patients "in need of tranquilizing drug treatment," mixed diagnoses not including regressed, nonreactive chronic schizophrenia[b] | Thioridazine (600 mg/day) plus chlordiazepoxide (N=54, 30 mg/day) or placebo (N=58) for 32 days |
| Holden et al., 1968 (12) | 22 | Chronic schizophrenia[b] | Thioridazine (300–500 mg/day) alone, thioridazine (150–250 mg/day) plus chlordiazepoxide (30–50 mg/day), and placebo for 8 weeks each |
| Michaux et al., 1966 (36) | 72 | Newly admitted, acutely ill psychiatric patients, "predominantly schizophrenic"[b] | Chlorpromazine (>300 mg/day) plus chlordiazepoxide (N=37, 30 mg/day) or placebo (N=35) for 28 days |

[a] Twelve reported previously by Wolkowitz et al. (23); of the five additional patients, two clinically responded to alprazolam.
[b] Diagnostic criteria not cited.
[c] Patients who had akathisia or whose anxiety was relieved by antiparkinsonian medication were excluded.

**TABLE 3 (continued)**

| Design | Results |
|---|---|
| Crossover | Mild but significant decrease in psychosis with alprazolam; responders (N=7) also had significant or nearly significant decreases in anxiety and depression; nonresponders had no change in psychosis but increases in anxiety and depression |
| Crossover | With lorazepam, minimal improvement in psychosis or anxiety but large decrease in depression, which persisted after lorazepam withdrawal; with alprazolam, rapid increase in paranoia and anxiety |
| Crossover | Significant decreases in psychosis and positive symptom ratings with alprazolam; responders also showed decreases in negative symptom ratings; response correlated with baseline anxiety, psychosis, age, prefrontal cortex atrophy (on CT scan), and alprazolam-induced decreases in plasma HVA |
| Between groups | During the first weeks of study, alprazolam but not diazepam was superior to placebo in reducing negative (but not positive) symptoms; neither was superior to placebo by weeks 4–5 |
| Between groups | Clonazepam resulted in earlier (week 1) improvement, mainly in anxiety, tension, and excitement; by week 4 no significant differences except in excitement and akathisia |
| Placebo crossover; single-blind administration plus blind rating of edited videotapes | Of nine patients who allowed videotaping, six were "much" or "very much" improved (Clinical Global Impression) |
| Placebo crossover | No significant effects on thought disorder, withdrawal, paranoia, anxiety, depression, or activity; four patients had aggressive behavior (two during or after clonazepam withdrawal) |
| Placebo crossover | In first 3-week period, both placebo and estazolam produced improvement in global assessments, but estazolam was superior in the second and third 3-week periods; estazolam was significantly superior for auditory hallucination frequency, visual hallucinations, and compulsive thoughts |
| Placebo crossover | Diazepam mildly but significantly better than placebo on BPRS total ratings, suspiciousness, and unusual thought content |
| Between groups | Significant effect of camazepam on anxiety, tension, irritability, aggressivity, and psychomotor unrest but no significant effect on delusions or hallucinations |
| Placebo crossover | No overall clinical benefit from diazepam, although one patient with high level of motor tension may have benefited |
| Multiple crossover (intensive design) | Three patients showed rapid and significant improvement with chlordiazepoxide; in two the improvement was "striking"; anxiety, hallucinations, suspiciousness, and unusual thought content improved; two patients showed no change in any rated area and one showed a nonsignificant increase in depression; initial anxiety level was directly correlated with clinical improvement |
| Between groups | In each week lorazepam produced significantly more improvement than placebo in anxiety, insomnia, delusions, hallucinations, behavior, fear, agitation, and global clinical assessment and nonsignificantly more improvement in Hamilton anxiety score |
| Between groups | Chlordiazepoxide attenuated the beneficial effects of fluphenazine on ward behavior scores and global ratings |
| Between groups | Slight antianxiety effect of chlordiazepoxide on global and target symptom ratings at 2 weeks but overall equivalent or poorer outcome at 4 weeks compared with placebo |
| Crossover | Chlordiazepoxide plus thioridazine superior to thioridazine alone only in isolated symptom clusters—disturbance of person, thought content, and motor behavior—and in 15 of 132 psychopathology items, including anergia, autism, passivity, and negativism |
| Between groups | Chlordiazepoxide significantly worse for schizophrenic disorganization, especially in women, but superior for thought disorder, ward behavior, and target symptoms in the 20% sickest patients and in patients with high baseline agitation or retardation |

receptor sensitivity), commonly seen with benzodiazepines, may obfuscate a relationship between plasma benzodiazepine concentration and clinical response (53, 54).

### *Response Specificity*

Several different uses of benzodiazepines in the treatment of schizophrenia have been conceptualized, ranging from acute anxiolysis or stress reduction and acute control of psychotic agitation through longer-term management of psychotic symptoms and/or reduction in the required doses of concomitantly administered neuroleptics (55). Several of the studies reviewed here indicated that benzodiazepines ameliorate anxiety, tension, hostility, and irritability in schizophrenic patients (8, 9, 16, 17, 22, 25, 30, 32, 33), and some showed significant reductions in depressive symptoms as well (9, 12, 16, 22). Several studies have also suggested that benzodiazepines significantly reduce core psychotic symptoms, such as hallucinations, delusions, and thought disorder (8, 9, 11, 17, 22, 23, 28, 29, 32, 33), although in other studies benzodiazepines had detrimental effects or attenuated the therapeutic effects of neuroleptics in some patients (4, 8, 22, 28, 34–36, 56, 57). Pato et al. (22) provided preliminary evidence that the responsivity of psychotic symptoms to benzodiazepines in individual patients is associated with responsivity of other symptoms, such as anxiety and depression, suggesting a broad distinction between benzodiazepine responders and nonresponders.

Several authors have also commented on the beneficial effects of benzodiazepines on negative symptoms, such as lack of spontaneity, emotional withdrawal, blunted affect, passivity, apathy, and negativism (8, 9, 12, 16, 23, 24, 49). We and others have noted rapid (within 1–2 weeks) and occasionally striking improvements in social relatedness, affability, spontaneity, humor, and interest in family and social life in some benzodiazepine-treated schizophrenic patients (8, 9, 23, 46, 47, 49, 51, 58–60).

In addition, benzodiazepines may ameliorate motor disturbances (e.g., motor unrest and agitation) (12, 30, 31, 33, 36), psychogenic or neuroleptic-induced catatonia in both schizophrenia and bipolar affective disorder (61 and unpublished work of H.K. Manji and T.A. Hurwitz, 1987), and akathisia or other extrapyramidal symptoms (25, 30, 62–64). Such effects may secondarily reduce psychotic-like symptoms, and it is not known to what extent they account for the antipsychotic effects observed (64, 65).

Finally, several open-label or retrospective studies have suggested an important role for benzodiazepines (combined with neuroleptics) in the acute management of psychotic agitation or disruptive, dangerous behavior. Salzman et al. (66, 67), Arana et al. (4), and Garza-Treviño et al. (68) reported that mean and/or total neuroleptic doses were lower in patients receiving neuroleptics plus lorazepam than in those receiving neuroleptics alone, raising the possibility that lorazepam enhanced neuroleptic efficacy (67).

## CLINICAL CONSIDERATIONS

As with any treatment, the benefits of benzodiazepine therapy must be weighed against its risks. Sedation, ataxia, and cognitive impairment are all possible side effects of benzodiazepines, especially with high doses, although clinical improvement may be seen at doses below those associated with sedation (23). Some patients exhibit behavioral disinhibition or psychotic exacerbation during benzodiazepine treatment (4, 8, 22, 23, 27, 34–36, 56, 57), so close clinical monitoring of patients is essential, especially in outpatient settings. Indeed, outpatients may be at greater risk for these reactions and for sedation-associated dysphoria (22, 57, 69). Patients may also experience a transient increase in symptoms (rebound) after benzodiazepine withdrawal (8, 23, 27, 70). It is currently recommended that benzodiazepine tapering be done very gradually, especially after prolonged benzodiazepine treatment or treatment with high-potency benzodiazepines with short half-lives. For these reasons, patients who are likely to be poorly compliant with medication regimens are generally poor candidates for other than very short-term benzodiazepine treatment. Benzodiazepines may also lead to physiological dependence or to abuse (66, 71–74). The risk of abuse in therapeutic settings is judged to be small, although the risk is somewhat higher in individuals with histories of multiple drug abuse (72, 73). The risk of benzodiazepine dependence in patients with schizophrenia is unknown but may be lower than in patients with nonpsychotic illnesses (74). Last, most of the studies reviewed here assessed benzodiazepine effects for less than 8 weeks; data on more prolonged or maintenance therapy are scanty and largely anecdotal. Indeed, Salzman (66) and Chouinard (71) recommended against the routine or maintenance use of benzodiazepines for the prevention of disruptive behavior or for the treatment of psychotic symptoms in schizophrenia.

The following conclusions seem probable but must remain tentative until more definitive studies are completed.

1. Response to benzodiazepines varies widely between patients; approximately 30%–50% of individual patients show favorable responses.
2. The magnitude of therapeutic response, when seen, is often modest but may be striking in certain patients.
3. Benzodiazepines are more effective when added to neuroleptics but may be mildly efficacious in certain patients when used alone.
4. Higher doses of benzodiazepines may be associated with better responses, although therapeutic effects may be seen in the range of commonly prescribed doses.
5. Different clinical patterns are emerging in the cur-

rent use of benzodiazepines for schizophrenia. Sedation and reductions in anxiety and agitation may be the most prominent effects, and the acute management of psychotic agitation or disruptive behavior is the most well-founded indication for adjunctive benzodiazepine use. However, significant reductions in positive and negative psychotic symptoms and normalization of certain motor disturbances are also observed in some patients.

6. Therapeutic effects, when seen, may develop rapidly—within hours, days, or 1–2 weeks. Some responsive patients evidence behavioral tolerance to the therapeutic effects of benzodiazepines in several weeks, although some patients show longer-lasting responses.

7. Predictors of clinical response are unclear at this time, although patients with high initial anxiety, psychosis, or motor disturbance may be the most likely to respond. In the following section, we examine possible predictors of clinical response.

## PATIENT RESPONSIVITY

### *Variability of Response*

In their 1986 review of the literature, Arana et al. (4) found that schizophrenic patients have an overall rate of response to benzodiazepines of approximately 30%–36%. In our review of the literature, which included more recent studies, we found a mean response rate of 48.7% (range=12%–83%) among patients in the 15 studies that reported response rates (8, 9, 12–14, 16, 17, 20, 22, 23, 26, 28, 31, 32, 36). We and others (2, 22, 23, 47) have remarked on the high degree of interindividual variability in response to benzodiazepine treatment among schizophrenic patients.

Consideration of the mechanisms by which benzodiazepine action can be terminated may yield some clues as to individual variability in response. For example, benzodiazepine action may be terminated by acute receptor adaptation (tolerance) or by changes in body distribution or clearance (elimination) (53). Other pharmacokinetic factors that may relate to response variability include differences in metabolic enzyme activity, the presence of active metabolites, and instability of drug levels over time.

An alternative approach to understanding individual variability posits the existence of behaviorally or biologically distinct subgroups of patients, which differ in susceptibility to benzodiazepines. This possibility would be supported by evidence of the reproducibility of therapeutic effects within individual patients over time or by the ability of certain behavioral or biological variables to predict treatment response. Few studies have examined whether benzodiazepine responsivity is a state or trait phenomenon. Kellner et al. (32) and Kirkpatrick et al. (48) suggested that some but not all schizophrenic patients who initially respond to benzodiazepines continue to show favorable responses when the same benzodiazepines are readministered.

### *Predictors of Response*

Several groups have found that patients with more prominent initial psychotic and/or anxiety or panic symptoms or with high levels of motor tension, agitation, or retardation respond more favorably to benzodiazepines (23, 31, 32, 36, 59), although one study failed to show such a relationship (35). Some (8), but not all (28), authors have also reported that prior neuroleptic response predicts response to benzodiazepines. The predictive value of sex and age in benzodiazepine-treated patients remains unclear (23, 28, 36). The results of two open-label studies suggested that relatively stable neuroleptic-responsive outpatients or outpatients with postpsychotic depression may respond more poorly to benzodiazepine augmentation or have difficulty tolerating the sedating side effects (57, 69). Adan and Siris (69) also suggested that inpatient status, which is associated with a more stimulating environment, more staff attention, and closer monitoring of dose and side effects, may interact favorably with benzodiazepine augmentation.

Biochemical predictors or concomitants of response have been investigated. Therapeutic response to neuroleptics alone is directly correlated with the magnitude of neuroleptic-induced decreases in plasma levels of homovanillic acid (HVA), a dopamine metabolite (75–78). Similarly, in our pilot study of alprazolam (23), the clinical responders showed significant alprazolam-associated decreases in plasma HVA levels, whereas the nonresponders actually showed increases in plasma HVA levels. The alprazolam-associated reductions in plasma HVA levels were directly correlated with reductions in ratings of both positive and negative schizophrenic symptoms. Such preliminary data suggest that dopamine system responsivity to benzodiazepines may underlie, or at least be associated with, therapeutic response to benzodiazepines in schizophrenic patients.

In the same pilot study (23), patients with radiographic signs consistent with greater prefrontal cortical atrophy (but without signs consistent with greater generalized atrophy) showed more therapeutic response to alprazolam augmentation. Such radiographic signs were also significantly correlated with alprazolam-associated reductions in plasma HVA levels. Although these findings are preliminary and their significance uncertain, they suggest that benzodiazepine actions in the stress- and benzodiazepine-sensitive prefrontal cortex (79–81) may be important in their therapeutic actions in patients with schizophrenia.

In our review of the neurobiology of benzodiazepines, which follows, we attempt to integrate these clinically determined predictors into our discussion of the mechanisms of benzodiazepine action.

## NEUROBIOLOGICAL CONSIDERATIONS

### *Benzodiazepines*

Benzodiazepines act in the CNS by binding to specific receptors (82) found in the highest concentrations in the cerebral cortex, hippocampus, amygdala, and certain discrete areas of the brainstem. Benzodiazepine binding to "central" benzodiazepine receptors, which are structurally and functionally linked to γ-aminobutyric $\text{acid}_A$ ($\text{GABA}_A$) receptors and to chloride ionophores, facilitates GABA neurotransmission and results in increases in permeability to chloride ions. The "opening" of these chloride channels permits a rapid influx of negatively charged chloride ions into the nerve cells, resulting in "hyperpolarization," i.e., a decrease in neuronal excitability. It should be noted that both benzodiazepine and GABA receptors are heterogeneous. "Peripheral" benzodiazepine receptors (which anatomically may be central or peripheral) are not coupled to GABA receptors or chloride ionophores (83). $\text{GABA}_B$ receptors are associated with adenylate cyclase, do not appear to be modulated by benzodiazepines, and are also not associated with chloride ionophores (84).

Benzodiazepine effects on neuronal excitability apparently mediate their anxiolytic, hypnotic, and anticonvulsant actions and may also underlie their inhibition of dopamine neurotransmission. In rats, benzodiazepines have been shown to decrease nigrostriatal dopamine release and turnover (85, 86), to block stress-induced activations in prefrontal cortical dopamine turnover (80), to attenuate acute neuroleptic-induced increases and augment chronic neuroleptic-induced decreases in dopamine turnover (87, 88, and unpublished work of F. Petty et al., 1987), and to potentiate the cataleptic effects of neuroleptics (88). (Catalepsy is a neuroleptic-induced effect in animals that is a functional consequence of dopamine receptor blockade [88].) One important exception to the general finding of benzodiazepine inhibition of dopamine turnover may occur in states of dopamine neuron "depolarization blockade." In such circumstances, dopamine neurons are overexcited to the point of inactivation (89, Manji and Hurwitz). Benzodiazepine-induced hyperpolarization might then reactivate the dopamine neurons in a dose-dependent manner; high enough doses of benzodiazepines, however, would further hyperpolarize the membrane, again inactivating it. Such a mechanism has been proposed to explain the efficacy of benzodiazepines in alleviating catatonic states in humans (Manji and Hurwitz).

Preclinical studies are also focusing on elucidation of the biological mechanisms of benzodiazepine tolerance and withdrawal (54, 90). Studies of the change in benzodiazepine receptor number after chronic benzodiazepine administration (54, 90) have yielded conflicting results: decrease, increase, and no change; in any event, such changes are unlikely to account for tolerance at clinically prescribed doses (54). Decreases in GABA receptor sensitivity after chronic benzodiazepine administration have also been reported (54, 90). Such changes or "downstream" changes, involving dopamine, norepinephrine, or serotonin system activities (54, 90), may be a prominent mechanism.

### *GABA*

GABA involvement in the effects of benzodiazepines may be particularly relevant in schizophrenia. Roberts (91) and others (52) have proposed a GABA hypothesis of schizophrenia, which postulates inadequate GABA inhibition of dopamine neurotransmission in this illness. The highest GABA levels in mammalian brain are located in the dopamine-rich basal ganglia. GABA-containing neurons there are intrinsic to the striatum, form a long feedback-loop path from the striatum to the substantia nigra pars reticulata and globus pallidus (i.e., from postsynaptic to presynaptic neurons), and constitute a major efferent pathway from the substantia nigra to the thalamus, superior colliculus, and reticular system (92). These tracts modify dopaminergic function in these and other sites by decreasing presynaptic dopamine release. In rats, GABAmimetic drugs also attenuate acute neuroleptic-induced activation of nigrostriatal and mesolimbic dopamine neurons (52, 85) and retard dopamine neuron postsynaptic responses to chronic neuroleptic blockade, e.g., supersensitivity and tolerance to catalepsy (84, 93). Further, inhibition of GABA input to dopamine neurons in the ventral tegmental area results in increased dopamine activity in the nucleus accumbens and olfactory tubercle and in behaviors suggestive of psychosis in cats (94). However, it must be noted that, as with benzodiazepines, GABA agonists may increase or decrease dopamine activity—depending on brain site, dose and duration of treatment, and possible activation of GABA-sensitive interneurons (95).

Despite the compelling preclinical data showing significant interactions between benzodiazepine/GABA systems and dopamine neurotransmission, CSF and plasma GABA levels have provided inconsistent evidence of GABA system hypofunctioning in schizophrenia (95–98). Reynolds et al. (99) recently reported, however, a lower than normal density of GABA uptake sites in hippocampus samples from the autopsied brains of schizophrenic patients; this deficit was correlated in the left hemisphere with higher than normal dopamine concentrations in the amygdala.

Clinical trials of GABA agonists in schizophrenia, including those with preferential affinity for $\text{GABA}_A$ or $\text{GABA}_B$ receptors, have been disappointing; only one out of 15 yielded positive results, and some indicated actual worsening of symptoms (84). Because of the complexity of GABA system functioning, the biphasic nature of GABAergic response (already described), and the imprecise pharmacologic spectrum of action of available GABA receptor agonists, these clinical data must be interpreted cautiously.

### *Rationales for Benzodiazepine Use in Schizophrenia*

Despite the largely negative clinical results with GABAmimetic agents, several rationales for the use of benzodiazepines in schizophrenia remain. Stress has been implicated as one mediator of relapse in schizophrenia (100), and an important objective in the long-term management of patients with schizophrenia is the reduction of environmental stress. Although GABA-mimetics are not remarkably effective anxiolytics, benzodiazepines show clear efficacy in this regard and represent a pharmacologic method for attenuating stress responses. Kirkpatrick et al. (48) and Sovner and Parnell-Sovner (101) recently reported that openly administered diazepam and buspirone, a nonbenzodiazepine anxiolytic, attenuated early signs of relapse or minimized stress-induced psychotic exacerbations in some schizophrenic patients.

Benzodiazepines may have more direct antipsychotic effects because of their inhibition of dopamine neurotransmission (86–88, 93, and Petty et al.), as we have discussed. Rapid decreases in presynaptic dopamine release may partially account for the observed rapidity of action of benzodiazepines in the treatment of some patients with schizophrenia. After several weeks of treatment with neuroleptics alone, presynaptic dopamine release (partially reflected in changes in plasma HVA levels in schizophrenic patients) decreases to below the baseline level (75, 76), perhaps secondary to depolarization blockade. Benzodiazepines used at this point may increase or decrease dopamine activity, depending on the degree of hyperpolarization achieved (Manji and Hurwitz). Such bidirectional responses may account for the variability of clinical response in schizophrenic patients and for the observation that plasma HVA levels may increase or decrease in parallel with clinical response in schizophrenic patients treated with a combination of alprazolam and fluphenazine (23). In addition, as already reviewed, GABAmimetics may retard the adaptation of postsynaptic dopamine neurons to neuroleptic blockade. If such effects in the mesolimbic dopamine tract also occur with benzodiazepines, they might further explain the efficacy of these drugs in augmenting neuroleptics for some patients.

Last, anatomic considerations may relate to benzodiazepine effects on dopamine activity. Several important dopamine tracts have been identified in the brain, including the nigrostriatal, the mesolimbic, and the mesoprefrontocortical tracts (89). Several characteristics of the mesoprefrontocortical tract differentiate it from the others. It has fewer autoreceptors or none and, perhaps as a consequence, in rats shows diminished acute and chronic responses to neuroleptics (89) and particular sensitivity to stress-activation, β-carbolines (benzodiazepine receptor inverse agonists), and benzodiazepines (79–81 and Petty et al.). Benzodiazepines may, therefore, be particularly effective in decreasing dopamine activity precisely in the dopamine tract in which neuroleptics are the least effective. Scatton et al. (102) found in rats that bilateral section of the corticostriatal projections or selective bilateral ablation of the frontal cortex resulted in lowered levels of nigral glutamic acid decarboxylase and in behaviors consistent with increased striatal dopamine transmission. These behaviors were reversed by administration of GABAmimetic agents. Similar effects from benzodiazepines administered to humans might explain a preferentially beneficial effect in patients who have radiographic signs consistent with prefrontocortical atrophy (23), although this observation remains preliminary.

Further delineation of responsive versus nonresponsive patient subgroups may advance our understanding of differences in pathophysiology in different groups of patients with schizophrenia. Because schizophrenia may be heterogeneous, it is surely worthwhile to explore any treatment that consistently benefits even a minority of otherwise treatment-resistant patients.

## RECOMMENDATIONS FOR FUTURE RESEARCH

With recent advances in clinical research methods and in basic science technology (90), our field is now poised for determining the role of benzodiazepines in the treatment of schizophrenia and the neurobiological underpinnings of their effects on this population. The unanswered questions that seem most important to us are 1) What clinical and biological features predict favorable and unfavorable response to benzodiazepines? 2) Are the therapeutic effects of benzodiazepines in schizophrenia related to their effects on the function of dopamine or other systems? 3) Which specific schizophrenic symptoms are most amenable to benzodiazepine treatment? and What can benzodiazepine treatment of negative symptoms teach us about the pathophysiology of such symptoms? 4) Should benzodiazepine use in schizophrenia be confined to short-term administration (e.g., for psychotic agitation), or is it suitable for maintenance treatment in certain responsive patients? and What underlies individual differences in the rate and extent of behavioral tolerance and can strategies be developed to avert such tolerance (54)? 5) When effective, will adjunctive benzodiazepine medication allow the use of lower neuroleptic doses in addition to enhancing clinical outcome? 6) What is the importance of benzodiazepine structure and potency, half-life, dose, plasma concentration, and spacing of drug administration in clinical response? Clinical studies are needed to systematically assess this last question. Further, it is advised that all reports cite the diagnostic criteria used in the study and the reliability of these criteria; multisystem diagnostic evaluations might prove especially revealing in delineating subgroups (103).

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# General Hospitals and the Severely Mentally Ill: Changing Patterns of Diagnosis

Mark Olfson, M.D.

*Objective: The author's goal is to determine whether there has been a recent change in the number and proportion of severely ill psychiatric patients treated in general hospitals. Method: He analyzed the discharge data from the National Hospital Discharge Survey for the years between 1970 and 1987, focusing particularly on the discharges of patients with psychiatric versus nonpsychiatric diagnoses. The number and proportion of discharges of patients with psychiatric diagnoses in four major diagnostic groups (depression, bipolar spectrum disorders, schizophrenia, and other psychoses) were determined. Results: Between 1970 and 1987, discharges of patients with psychiatric diagnoses from general hospitals increased by a factor of 0.8. The percentage of discharges of patients with the diagnoses of depression (18.0%–22.7%), schizophrenia (9.4%–13.6%), and paranoid or other nonorganic psychoses (3.1%–4.0%) remained relatively constant. The percentage of discharges of patients with the diagnosis of nondepressed bipolar disorder increased from 0.6% in 1970 to 3.2% in 1987. Conclusions: Although there has been a recent absolute increase in the number of general hospital patients with severe psychiatric diagnoses, the increase has been tempered by a concomitant increase in the number of patients with nonsevere diagnoses. Changes in classification systems (DSM-II or ICDA-8 to DSM-III or ICD-9-CM) and questions regarding the rigor with which the nosologic changes have been incorporated into practice complicate the interpretation of these findings.*

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It is widely believed that an increasing proportion of psychiatric patients in general hospitals suffer from severe mental illness. Some general hospital clinicians have expressed concern that they are being forced to treat severely disabled patients who in earlier times would have been cared for in state mental hospitals (1, 2).

Support for the idea that general hospitals are treating more severely mentally ill patients than they used to comes from anecdotal reports and national data sets. At one general hospital, the proportion of psychiatric patients with histories of state hospital care more than doubled in less than a decade (3). At another general hospital, a majority of the frequent users of the inpatient service were reported to suffer from schizophrenia or bipolar disorder (4). Such reports bolster the perception that the psychiatric patients currently treated in general hospitals are more seriously ill than those treated in earlier years.

National data also provide evidence that general hospitals are becoming increasingly populated by severely ill psychiatric patients. A detailed analysis of data from the National Institute of Mental Health (NIMH) by Thompson et al. (5) confirmed that the proportion of general hospital psychiatric inpatients with severe mental illness (i.e., patients with schizophrenia, affective psychoses, paranoid states, or other nonorganic psychoses) increased from 38.8% to 47.7% between 1970 and 1980.

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**TABLE 1. Discharges of Patients With Mental Disorders From Short-Stay Nonfederal General Hospitals, 1970–1987[a]**

| | | Primary Diagnosis of Mental Disorder | | Severe Mental Disorder | |
|---|---|---|---|---|---|
| Year | All Discharges (thousands) | Discharges (thousands) | % of All Discharges | Discharges (thousands) | % of Discharges With Mental Disorder |
| 1970 | 29,127 | 986 | 3.4 | 192 | 19.5 |
| 1971 | 29,459 | 1,050 | 3.6 | 219 | 20.9 |
| 1972 | 31,627 | 1,176 | 3.7 | 223 | 19.0 |
| 1973 | 32,101 | 1,227 | 3.8 | 260 | 21.2 |
| 1974 | 34,372 | 1,352 | 3.9 | 274 | 20.3 |
| 1975 | 34,042 | 1,494 | 4.4 | 295 | 19.7 |
| 1976 | 34,372 | 1,485 | 4.3 | 316 | 21.3 |
| 1977 | 35,902 | 1,628 | 4.5 | 369 | 22.7 |
| 1978 | 35,616 | 1,730 | 4.9 | 399 | 23.1 |
| 1979 | 36,747 | 1,723 | 4.7 | 416 | 24.1 |
| 1980 | 36,832 | 1,692 | 4.6 | 393 | 23.2 |
| 1981 | 38,544 | 1,747 | 4.5 | 447 | 25.6 |
| 1982 | 38,594 | 1,746 | 4.5 | 462 | 26.5 |
| 1983 | 38,783 | 1,701 | 4.4 | 471 | 27.7 |
| 1984 | 37,162 | 1,690 | 4.5 | 512 | 30.3 |
| 1985 | 35,057 | 1,700 | 4.8 | 575 | 33.8 |
| 1986 | 34,256 | 1,807 | 5.3 | 612 | 33.9 |
| 1987 | 33,387 | 1,781 | 5.3 | 633 | 35.5 |

[a]Data are from the National Hospital Discharge Survey. Severe mental disorder is defined as 295–299 in *ICDA-8* and *ICD-9-CM*.

The current study explores the diagnostic composition of mentally ill patients discharged from general hospitals between 1970 and 1987. In contrast to the study by Thompson et al. (5), which focused on hospitals with psychiatric units, the current report analyzes a representative national sample of psychiatric patients from all nonfederal short-stay general hospitals. The results suggest that although general hospitals have experienced an absolute increase in the number of patients with severe psychiatric diagnoses, this increase has been accompanied by an increase in the number of patients with nonsevere psychiatric diagnoses. Furthermore, it is difficult to interpret the trends in reported diagnoses because of changes in diagnostic nomenclature.

## METHOD

The National Hospital Discharge Survey, compiled annually by the National Center for Health Statistics, selects a national probability sample of discharges from nonfederal hospitals that have an overall average length of stay of less than 30 days. Because approximately 95% of these facilities are general hospitals, they will be referred to as such. On the basis of this probability sample, the National Hospital Discharge Survey provides national estimates of the diagnostic, procedural, and demographic characteristics of patients treated at these facilities. In the present analysis, all data refer to the discharge diagnosis listed first.

When psychiatrists record discharge diagnoses, they generally use nomenclature from the current *DSM*. When hospitals report these diagnoses to federal agencies such as the National Center for Health Statistics, however, they use *ICD* diagnoses. Because the crosswalk between the *DSM* and *ICD* systems contains substantial discontinuities (6, 7), variation occurs in the process of translating *DSM* to *ICD* codes. A second potential source of uncertainty arises from the changes in the *ICD* and *DSM* diagnostic systems that have occurred over time. In 1979, *ICD-9* replaced *ICDA-8*, and in 1980 *DSM-III* replaced *DSM-II*. In the Results section, a brief discussion is presented of several classificatory discontinuities that have arisen because of changes in diagnostic nomenclature.

## RESULTS

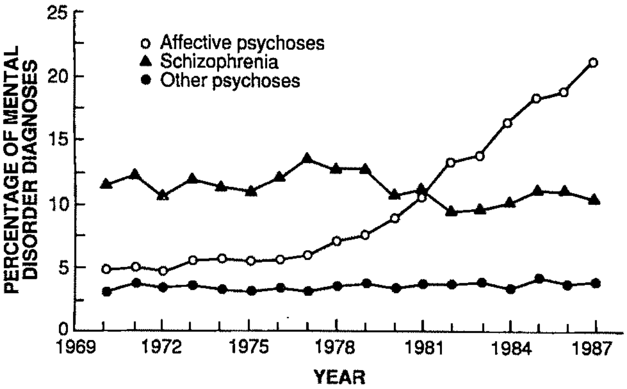
### *Inpatient Psychiatric Care*

In the years between 1970 and 1987 the number of general hospital discharges of patients with primary psychiatric diagnoses increased by 0.8 (table 1). This growth was concentrated in the years between 1970 and 1978; there was very little subsequent growth (table 1). The increase in discharges of patients with psychiatric diagnoses occurred within the context of a more modest growth of all discharges. All discharges grew by 0.3 between 1970 and 1983 before falling off slightly over the following 4 years. Because of the faster growth rate of discharges of patients with psychiatric diagnoses, the percentage of the total general hospital discharge diagnoses represented by psychiatric disorders grew from 3.4% in 1970 to 5.3% in 1987.

### *The Severely Mentally Ill*

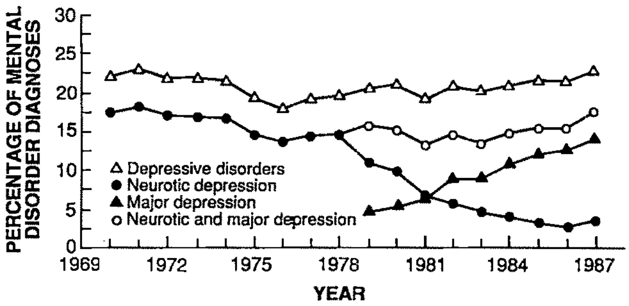
Between 1970 and 1987, the number of general hospital patients discharged with what Thompson et al. (5) defined as severe mental disorder diagnoses (schizophrenia, affective psychoses, paranoid states, and other

**FIGURE 1. Discharges of Patients With Severe Psychiatric Disorders From Short-Stay Nonfederal General Hospitals, 1970–1987**[a]



[a]Data are from the National Hospital Discharge Survey. Affective psychosis is code 296 in *ICDA-8* and *ICD-9-CM*. Schizophrenia is code 295 in *ICDA-8* and *ICD-9-CM*. Other psychoses include codes 297–299 in *ICDA-8* and *ICD-9-CM*.

**FIGURE 2. Discharges of Patients With Depression From Short-Stay Nonfederal General Hospitals, 1970–1987**[a]



[a]Data are from the National Hospital Discharge Survey. Depressive disorders include codes 296.0, 296.2, 298.0, and 300.4 in *ICDA-8* and 296.2, 296.3, 296.5, 298.0, 300.4, and 311 in *ICD-9-CM*. Neurotic depression is code 300.4 in *ICDA-8* and *ICD-9-CM*. Major depression includes codes 296.2 and 296.3 in *ICD-9-CM*.

nonorganic psychoses—295–299 in *ICDA-8* and *ICD-9-CM*) grew by an estimated 2.3 (table 1). This growth increased the percentage of total general hospital discharges of patients with severe mental disorder diagnoses from 19.5% in 1970 to 35.5% in 1987.

When the overall increase in discharges of patients with severe psychiatric diagnoses is disaggregated into the three major diagnostic categories, the growth was found to occur almost exclusively among the affective psychoses (figure 1). Moreover, the increase occurred almost entirely during the *DSM-III* and *ICD-9-CM* era. A closer examination of this finding reveals that classificatory changes may be responsible for a substantial proportion of this increase.

### *Depression*

According to the National Hospital Discharge Survey data, the number of general hospital discharges of patients with diagnoses of depressive disorders (codes 296.0, 296.2, 298.0, and 300.4 in *ICDA-8* and 296.2, 296.3, 296.5, 298.0, 300.4, and 311 in *ICD-9-CM*) increased from 218,000 in 1970 to 405,000 in 1987. Because of parallel increases in discharges of patients with other psychiatric diagnoses, the percentage of discharges of patients with diagnoses of depressive disorders remained relatively constant—18.0% in 1976 and 22.7% in 1987.

During the years under study, there was a marked change in the specific diagnostic composition of the depressed inpatients. During the *ICD-9-CM* period, the proportion of discharges of patients with diagnoses of neurotic depression (code 300.4) declined and a compensatory increase occurred in discharges of patients with diagnoses of major depressive disorder (codes 296.2 and 296.3). The proportion of discharges of patients with other depressive diagnoses (*ICDA-8* codes 296.0 [involutional melancholia], 296.2 [manic-depressive psychosis, depressed], and 298.0 [reactive depressive psychosis] and *ICD-9-CM* codes 296.5 [bipolar affective disorder, depressed], 298.0 [depressive type psychosis], and 311 [depressive disorder not elsewhere classified]) remained essentially unchanged (figure 2). To help clarify these time trends, a brief review is presented of some salient intervening modifications in the classification of depression.

One of the most common diagnoses in *DSM-II* and *ICDA-8* was neurotic depression. Because its clinical criteria were found to be overly broad and lacking in conceptual clarity (8, 9), *DSM-III* abandoned neurotic depression (*DSM-II* code 300.4). In its place, *DSM-III* defined a new diagnosis, dysthymic disorder (code 300.40), a low-grade unipolar depression of long duration. Dysthymic disorder was conceptually much narrower than the older neurotic depression, and over time dysthymia according to *DSM-III* (neurotic depression according to *ICD-9-CM*) was less often diagnosed.

A second change in the classification of depression was the creation in *ICD-9-CM* and *DSM-III* of major depressive disorder (codes 296.2 and 296.3). This diagnosis was broader than its *ICDA-8* or *DSM-II* predecessor manic-depressive psychosis, depressed type (code 296.2). Manic-depressive psychosis, depressed type, was a chronic condition, but major depressive disorder required only a 2-week period of affective symptoms. Soon after its introduction, major depressive disorder became the most common diagnosis of depression in inpatient general hospital psychiatry.

Thompson et al. (5) excluded patients with neurotic depression from their count of the severely mentally ill. When *DSM* criteria are rigorously applied, a substantial number of patients with *DSM-II* neurotic depression meet criteria for *DSM-III* major depression (10). Excluding patients with neurotic depression, therefore, may result in underestimating the number who suffer from severe illness. At the same time, however, including all patients with major depression diagnosed according to *DSM-III* or *ICD-9-CM* among counts of the severely mentally ill may render estimates spuriously high. With the present data, there is no reliable means of discriminating the depressed inpatients with severe as opposed to nonsevere conditions.

### *Bipolar Spectrum Disorders*

*ICDA-8* did not distinguish severely depressed patients who had had previous manic episodes from those who had not had such episodes. For this reason, it is not possible to estimate the number of discharges during the *ICDA-8* period of patients who suffered from an illness equivalent to bipolar disorder as defined in *DSM-III* or *ICD-9-CM*. However, an approximate equivalency exists between individuals diagnosed in the *DSM-II* and *ICDA-8* period as having manic-depressive illness, manic type (code 296.1), or manic-depressive illness, circular type (code 296.3), and those diagnosed in the *DSM-III* and *ICD-9-CM* period as having bipolar disorder, manic (code 296.4), or bipolar disorder, mixed (code 296.6). Silverstein et al. (10) found that more than 80% of patients who met criteria for either *DSM-II* diagnosis (codes 296.1 and 296.3) also met criteria for one of the *DSM-III* diagnoses (codes 296.4 and 296.6).

The number of patients with nondepressed bipolar spectrum disorders increased markedly from an estimated 6,000 discharges in 1970 (0.6% of the discharges of patients with psychiatric diagnoses) to 57,000 discharges (3.2% of the discharges of patients with psychiatric diagnoses) in 1987.

### *Schizophrenia*

The proportion of psychiatric patients discharged with schizophrenic diagnoses remained essentially constant between 1970 and 1987. As shown in figure 1, the percentage of mentally ill patients with schizophrenia ranged from a high of 13.6% in 1977 to a low of 9.4% in 1982. Because of the absolute increase in the number of discharges of patients with psychiatric diagnoses over time, the number of patients with a primary discharge diagnosis of schizophrenia increased from 128,000 in 1970 to 185,000 in 1987.

The subtypes of schizophrenia in *DSM-II* match those in *ICDA-8*. In the shift from *ICDA-8* to *ICD-9-CM*, there were no substantial modifications. However, the transition from *DSM-II* to *DSM-III* included several classificatory changes that narrowed the spectrum of disorders in the schizophrenia group. For example, *DSM-III* classified patients with a short total duration of symptoms as having schizophreniform disorder (code 295.40), but the *ICD-9-CM* classification would be acute schizophrenic episode (code 295.4). *DSM-III* classified patients with low-grade and stable schizophrenic spectrum symptoms as having schizotypal personality disorder (code 301.22), but *ICD-9-CM* continued to use the simple schizophrenia classification (code 295.0). *DSM-III* also created a category for mixed and atypical conditions (schizoaffective disorder, code 295.70), but *ICD-9-CM* continued to use the classification schizophrenia, schizoaffective type (code 295.7). For the most part, these classificatory changes did not move substantial numbers of patients either into or out of the broad category of schizophrenia under *ICDA-8* or *ICD-9-CM*.

In addition to changes in classification, *DSM-III* also included changes in the definition of schizophrenia. Perhaps the most important of these was the exclusion of patients with a full affective syndrome before the onset of psychotic symptoms. Possible consequences of this change are addressed in the Discussion section.

### *Paranoid Disorder and Other Nonorganic Psychoses*

The proportion of discharges from general hospitals of patients with psychiatric diagnoses represented by patients with paranoid disorders or other nonorganic psychoses (*ICDA-8* and *ICD-9-CM* codes 297–299) remained essentially unchanged between 1970 and 1987. The proportion of discharges of patients with paranoid disorders or other nonorganic psychoses ranged from 3.1% to 4.3% (other psychoses in figure 1).

In these two quantitatively minor disease categories, the diagnoses in *ICDA-8, ICD-9-CM,* and *DSM-II* differ only in detail from one another. The changes from *DSM-II* to *DSM-III,* although conceptually more substantial, did not appreciably influence the distribution of discharge diagnoses.

## DISCUSSION

During the 1970s and middle 1980s there was an impressive expansion in the volume of inpatient psychiatric patients treated in general hospitals. The proportion of general hospital patients given psychiatric diagnoses increased by more than half, and their absolute number nearly doubled. At the same time, the occupancy rate in nonfederal short-stay hospitals fell from 78.0% in 1970 to 64.9% in 1987 (11). General hospital administrators, perhaps in an effort to fill empty beds, chose to expand their provision of inpatient psychiatric services. However, concern soon developed that the patients receiving treatment in general hospitals were becoming more severely ill.

The current analysis confirms that in fact there has been a recent increase in the number of psychiatric general hospital inpatients with severe diagnoses. However, this increase has been nearly balanced by increases in patients with nonsevere psychiatric diagnoses. Specifically, the proportion of general hospital patients diagnosed as suffering from depression, schizophrenia, paranoid psychoses, and other nonorganic psychoses has remained relatively constant. One notable exception to this trend is a recent increase in the proportion of general hospital psychiatric patients diagnosed with nondepressed bipolar conditions. Because of changes in classification it is not possible to discern whether this increase represents a reclassification of patients who in an earlier era would have received other diagnoses (12) or whether this growth represents an actual increase in the treated prevalence of patients with mania and related affective conditions (13).

The observed stable proportion of schizophrenic inpatients runs counter to reports that the diagnosis of schizophrenia has recently become less common (14, 15). At one major university hospital, the percentage of patients diagnosed with schizophrenia fell by nearly half in the decade surrounding the change from *DSM-II* to *DSM-III* (14). A similar trend has been noted at Veterans Administration inpatient facilities (15). These reports, which are in accord with the conceptual narrowing of schizophrenia (12, 16), appear to be in conflict with the current finding that the proportion of schizophrenic inpatients in general hospitals has remained nearly constant. One explanation for this apparent contradiction is that the changes in diagnostic criteria embodied in *DSM-III* have had a substantially greater impact on university-affiliated hospitals than on hospitals without university affiliation. Surveys of U.S. psychiatrists demonstrate that the criteria actually used to diagnose schizophrenia have been relatively uninfluenced by the change from *DSM-II* to *DSM-III* (17–19).

When the diagnostic practices of psychiatric residents and psychiatrists have been compared, residents have been found to be more heavily influenced by the changes introduced in *DSM-III* (19). At university hospitals, where residents make a large proportion of the diagnoses, changes in nosology would be expected to have a substantial impact on the pattern of recorded diagnoses. In a national sample, such as in the current study, the diagnostic practices of residents may be diluted by those of established psychiatrists, which are less sensitive to nosologic developments.

A second explanation is that the observed constant proportion of discharges of patients with schizophrenia diagnoses conceals an underlying increase in the number of patients who would be diagnosed as suffering from schizophrenia by the older, less restrictive *DSM-II* criteria. This explanation hypothesizes that psychiatrists did in fact tighten their criteria for schizophrenia under *DSM-III*, but that this change was offset by a more severely ill patient population. One consequence of these events would be an accumulation of discharges of patients with psychotic diagnoses other than schizophrenia. This supposition is consistent with the notion that the increase in discharges of patients with nondepressed bipolar diagnoses is attributable to a reclassification of patients who in the earlier period would have been given a diagnosis of schizophrenia.

Diagnosis is only a rough index of the severity of illness. Functional disability and duration of illness are other key dimensions that are not measured in the current study (20). Some patients may have "severe diagnoses," but it may be misleading to categorize them as severely mentally ill because their course of illness is not prolonged or seriously impairing. On the other hand, many individuals, such as those with severe personality disorders or substance use disorders, may experience severe disabling illnesses. A more complete assessment of the severity of illness should also take into account the extent and availability of social supports and economic resources.

A somewhat broader perspective on the composition of general hospital psychiatric inpatient admissions can be gleaned from the periodic sample surveys conducted by NIMH. These surveys reveal that between 1980 and 1986, the percentage of involuntary admissions (15.8% in 1980 and 15.3% in 1986) and the percentage for which no payment was expected (3.6% in 1980 and 3.4% in 1986) remained essentially constant while the percentage of admissions with previous psychiatric hospitalizations (70.1% in 1980 and 62.6% in 1986) actually declined (unpublished data from the Statistical Research Branch, Division of Applied and Services Research, NIMH). Unfortunately, comparable data from earlier years are not available, and the NIMH surveys do not sample general hospital psychiatric patients treated outside of psychiatric units. However, these data do support a stability in the severity of illness of the psychiatric patient population treated in general hospitals between 1980 and 1986.

The complexities that surround the assessment of the severity of illness make clear that isolated diagnoses are of limited descriptive value. Future utilization surveys should include a wide range of easily obtained measures of the severity of illness that are based on readily observable events and behaviors. Knowledge of variables such as route of admission (emergency room, direct, or transfer), housing status before admission, global level of functioning (axis V from *DSM-III-R*), and treatment status before admission would increase our understanding of who receives treatment. A more precise picture of who receives inpatient care will in turn better inform mental health service planning.

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# Stressful Life Events and Symptom Onset in HIV Infection

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*Objective: The authors' goal is to provide basic epidemiologic data on the issue of reactivity to stress and HIV symptom onset by studying the relationship between a broad set of naturally occurring stressor events and HIV natural history in a large longitudinal community sample of HIV-seropositive homosexual men. Method: Subjects were recruited from a cohort of 1,011 homosexual men enrolled in the Chicago site of the Multicenter AIDS Cohort Study who also participated in the Coping and Change Study. The men were given self-administered questionnaires assessing behavioral, psychological, and psychosocial variables. Relationships between reports of stressful life events and longitudinal biomedical data measuring illness progression were examined. Life events were assessed by reports on the numbers of lovers, friends, and acquaintances who were diagnosed with AIDS or had died of AIDS and by scores on a checklist of 24 more general serious stressor events. The variables indicating progression of illness among initially asymptomatic men were a drop in T-helper lymphocyte percent (CD4%) between pairs of examinations of at least 25% and onset between examinations of thrush and/or fever lasting a minimum of 2 weeks. Results: The authors found no evidence that serious stressor events have any meaningful effect on symptom onset indicated by either a drop in CD4% or onset of fever or thrush. Conclusions: There is no need for asymptomatic people with HIV infection to restrict their lives in order to avoid exposure to stressful life experiences or to develop special skills for coping with stress to forestall the progression of HIV illness.*

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There is currently a great deal of scientific interest in the possibility that stressful life experiences are capable of altering the course of HIV infection by influencing immune function (1). Although there is little direct evidence for this possibility, the urgency of the problem has led to the development of several stress inoculation interventions aimed at improving host resistance among HIV-seropositive homosexual men (2; unpublished 1988 study of M.A. Fletcher et al.). Furthermore, a great many homosexual men, aware of the possibility that reactivity to stress might influence the course of HIV infection, have invested in books, tapes, and classes that purport to teach methods of influencing immune function by controlling stress (3). The scientific basis for suspecting that stress might affect the course of HIV infection is found in research documenting an effect of stress on the course of herpes virus infection (4–8). Certain similarities between HIV and herpes viruses have led to the suggestion that similar reactivity to stress might be found for HIV. For example, both HIV and herpes viruses are capable of latent infection, and analogous methods of reactivation have been demonstrated (1). Furthermore, in vitro studies have provided direct evidence of possible stress-mediated initiation of HIV replication (9).

In the light of this provocative laboratory evidence, one would expect to find many epidemiologic researchers examining the relationship between stress and course of HIV infection in naturalistic studies. However, T.J. Coates et al. (unpublished 1989 study) are, to our knowledge, the only investigators to have examined this association. Their results documented that HIV-seropositive homosexual men who reported the death of friends and lovers from AIDS were more likely than men who did not experience these losses to have subsequent increases in HIV-related symptoms over a follow-up period of several years. Illness progression was particularly pronounced among men who

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reported the most extreme grief reactions. On the basis of this evidence, Coates et al. called for clinical trials to develop effective stress intervention programs among HIV-seropositive individuals.

A limitation that makes it difficult to interpret the results of this study unequivocally is that the measure of stress (death of friends and lovers from AIDS) is also an indicator of involvement with HIV-infected individuals and, possibly, risky sexual practices. This involvement may be associated with earlier infection. Since duration of infection is known to be the best predictor of AIDS onset, this confounding could readily explain the relationship found by Coates et al. (unpublished 1989 study) between stress and course of illness. An obvious solution to this problem would be to study the effects of stresses that are not confounded in this way. This is the purpose of the present report, which examines the relationship between a broad set of naturally occurring stressor events and HIV natural history in a large longitudinal community sample of HIV-seropositive homosexual men.

## METHOD

Participants in this study were recruited from a cohort of 1,011 homosexual men enrolled in the Chicago site of the Multicenter AIDS Cohort Study. The Multicenter AIDS Cohort Study is a collaborative biomedical study designed to investigate the natural history of AIDS by collecting semiannual medical and laboratory data from participants (10). Additionally, Chicago site subjects were invited to participate in the Coping and Change Study, an investigation of psychosocial issues funded by the National Institute of Mental Health. Those agreeing to participate were given a self-administered questionnaire shortly after each Multicenter AIDS Cohort Study examination to assess a wide range of behavioral, psychological, and psychosocial variables. More than 98% of the subjects in the Multicenter AIDS Cohort Study also participated in the Coping and Change Study. The mean age of these subjects was 35 years at recruitment. Their mean educational level was 16.5 years; 93% were white non-Hispanic, and their mean income was approximately $25,000 (1984–1985 dollars).

Although blood samples were obtained at each Multicenter AIDS Cohort Study visit, serologic test results were not available until between waves 4 and 5, which means that very few of the men knew their serologic status during the first 2 to 3 years of the study, the time interval covered in this report. Men who were seropositive at baseline were, on average, approximately 2 years younger than seronegative men ($t=3.4$, $df=778$, $p<0.01$), had approximately 1 year less education ($t=6.5$, $df=753$, $p<0.01$), and were 5% less likely to be white ($t=2.3$, $df=749$, $p<0.02$).

The current investigation examines relationships between reports of stressful life events (obtained in the Coping and Change Study psychosocial questionnaires) and longitudinal biomedical data measuring illness progression (obtained in the Multicenter AIDS Cohort Study examination). Life events were assessed in two different series of questions. In the first, subjects in each wave were asked to report the numbers of lovers, friends, and acquaintances who were diagnosed as having AIDS or had died of AIDS over the 6-month recall period (six separate reports). A summary count of all these AIDS diagnoses and/or deaths in the subject's social network was included as one measure of stress. Second, a checklist of 24 more general serious stressor events (e.g., foreclosure of a mortgage, job loss, death of a parent) experienced over the same recall period was included in each wave. This checklist was developed on the basis of pilot research with focus groups of homosexual men and with the help of a community advisory panel (11). A summary count of all events reported on this checklist was included as the second measure of stress.

Two outcome variables were included to indicate progression of illness among initially asymptomatic HIV-seropositive men: 1) a decrease in T-helper lymphocyte percent (CD4%) between pairs of examinations of at least 25% of the value at the earlier examination and 2) onset between examinations of thrush and/or fever lasting a minimum of 2 weeks. Both symptoms have been shown to predict illness in longitudinal examination of AIDS onset (12, 13). These longitudinal investigations showed that reduction of CD4 is one of the most important prognostic indicators of progression of HIV infection and that CD4% is a better predictor than either the number of CD4 or the CD4-CD8 ratio (12). A CD4% drop of 25% or more among HIV-seropositive men is usually associated with progression of illness (14). Longitudinal investigations also show that thrush and fever are more reliable indicators of subsequent decline in functioning than other HIV-related symptoms (13). In an effort to limit the focus to the subsample of men with initially normal CD4 status, the analysis of drop in CD4% was restricted to men with baseline CD4% levels equal to or greater than the mean in the HIV-seronegative subsample (45%). The analysis of thrush and/or fever was restricted to men who reported neither symptom at wave 1. All HIV-seropositive individuals were seropositive at wave 1, and all HIV-seronegative individuals were consistently seronegative through wave 5. This means that the small number of men who seroconverted between waves 1 and 5 were excluded from the following analyses.

## RESULTS

### *Distributions of Symptoms*

Table 1 shows the conditional probabilities of symptom onset between waves 1 and 5 for subjects who were asymptomatic at wave 1 (i.e., those who had nor-

**TABLE 1. HIV-Seropositive and HIV-Seronegative Homosexual Men Who Experienced a CD4% Decrease or Developed Thrush and/or Fever During the Multicenter AIDS Cohort Study**

| | Seropositive | | | Seronegative | | |
|---|---|---|---|---|---|---|
| | Number Without Symptom at Earlier Wave | With Symptom at Later Wave | | Number Without Symptom at Earlier Wave | With Symptom at Later Wave | |
| Symptom | | N | % | | N | % |
| CD4% decrease of at least 25% | | | | | | |
| Between waves 1 and 2 | 61 | 21 | 34.4 | 235 | 14 | 6.0 |
| Between waves 2 and 3 | 22 | 2 | 9.1 | 204 | 6 | 2.9 |
| Between waves 3 and 4 | 13 | 1 | 7.7 | 37 | 2 | 5.4 |
| Between waves 4 and 5 | 12 | 3 | 25.0 | 8 | 2 | 25.0 |
| Between waves 1 and 5 | 108 | 27 | 25.0 | 484 | 24 | 5.0 |
| Development of thrush and/or fever | | | | | | |
| Between waves 1 and 2 | 302 | 22 | 7.3 | 329 | 13 | 4.0 |
| Between waves 2 and 3 | 284 | 22 | 7.7 | 356 | 28 | 7.9 |
| Between waves 3 and 4 | 252 | 22 | 8.7 | 347 | 11 | 3.2 |
| Between waves 4 and 5 | 221 | 18 | 8.1 | 52 | 2 | 3.8 |
| Between waves 1 and 5 | 1,059 | 84 | 7.9 | 1,084 | 54 | 5.0 |

mal CD4% levels at the earlier wave of each wave pair but whose CD4% decreased between examinations by 25% and those who had neither thrush nor fever at the earlier wave of each wave pair but who, between examinations, developed one and/or the other lasting a minimum of 2 weeks). The vast majority of the subjects who either experienced a decrease in CD4% or developed thrush and/or fever continued to have these symptoms throughout the rest of the study period. As a result, all subjects who became symptomatic during a particular wave were excluded from analyses in subsequent waves. For example, the two HIV-seropositive men who had a CD4% decrease between waves 2 and 3 represent 9.1% of the 22 men with normal CD4% levels at wave 2, and the one HIV-seropositive man who had a CD4% decrease between waves 3 and 4 represents 7.7% of the 13 men with normal CD4% levels at wave 3. The numbers of subjects in the CD4% analyses are much smaller than the numbers in the thrush/fever analyses because the number of men who already had abnormal CD4% levels at wave 1 (and were consequently excluded from the analyses) was considerably greater than the number with thrush and/or fever at wave 1.

As one would expect, the risk of developing each symptom was generally much higher among HIV-seropositive men than among HIV-seronegative men. The percentages within each of these groups (i.e., seropositive and seronegative men) were quite similar over time for thrush and/or fever, indicating that the risk for this type of symptom in this sample did not vary as a function of time since infection. The percentages were more variable over time for the decrease in CD4%. The most striking sign of this variability was the substantially higher percentage of HIV-seropositive men at waves 1 and 2 than at later intervals who experienced a 25% drop in CD4%. This change may represent an increasing robustness in the asymptomatic men between the initiation of the study (summer 1984) and the end of the fifth wave of data collection (winter 1987), or it might reflect a change in the risk of progression of illness at different times after initial infection. The absence of data on time of infection makes it impossible for us to discriminate between these two possibilities.

The distributions of stressor events are presented in table 2 for the same groups of men reported in table 1. In general, HIV-seropositive men reported more deaths from or diagnoses of AIDS in their social networks than did HIV-seronegative men. Furthermore, among the HIV-seropositive men, the comparatively more healthy men in the CD4% analysis—all of whom had normal CD4 levels at the earlier wave in which they were included—reported a much lower mean number of AIDS diagnoses and/or deaths in their social networks than did the HIV-seropositive men included in the thrush/fever analysis. Both of these patterns are consistent with the possibility that men who report more AIDS diagnoses and/or deaths in their social network are likely to have become infected at an earlier point in the epidemic. This would create a spurious association between these events and disease progression. In comparison, there were no meaningful differences among groups in mean number of other serious stressor events.

### *Relationship Between Stresses and Symptoms*

Logistic regression equations were estimated to examine the relationship between the occurrence of stressful life events and each of the two symptoms between waves 1 and 2, 2 and 3, 3 and 4, and 4 and 5. In each analysis, men who did not have the symptom at the earlier wave were analyzed to assess the impact of intercurrent life events on either drop in CD4% or onset of thrush and/or fever. All equations included controls for initial number of CD4, number of recent experiences of receptive anal intercourse, and condom use in an effort to remove the confounding influences of these exogenous variables on the relationship between stresses and symptoms.

Separate analyses of each wave-pair yielded results

TABLE 2. Measures of Stress in HIV-Seropositive and HIV-Seronegative Homosexual Men Who Experienced a CD4% Decrease or Developed Thrush and/or Fever During the Multicenter AIDS Cohort study

| | Seropositive | | | | Seronegative | | | |
|---|---|---|---|---|---|---|---|---|
| | AIDS Diagnoses and Deaths in Social Network[a] | | Other Serious Stressors | | AIDS Diagnoses and Deaths in Social Network[a] | | Other Serious Stressors | |
| Symptom | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| CD4% decrease of at least 25% | | | | | | | | |
| Between waves 1 and 2 | 1.15 | 3.29 | 1.03 | 1.48 | 0.56 | 2.58 | 0.98 | 1.32 |
| Between waves 2 and 3 | 0.32 | 0.57 | 0.77 | 1.51 | 0.98 | 2.17 | 0.92 | 1.16 |
| Between waves 3 and 4 | 1.62 | 2.22 | 0.62 | 0.96 | 0.70 | 1.94 | 0.78 | 1.25 |
| Between waves 4 and 5 | 0.58 | 1.16 | 0.17 | 0.58 | 0.25 | 0.71 | 1.13 | 1.65 |
| Between waves 1 and 5[b] | 0.97 | 2.65 | 0.83 | 1.38 | 0.74 | 2.35 | 0.94 | 1.25 |
| Development of thrush and/or fever | | | | | | | | |
| Between waves 1 and 2 | 1.43 | 4.23 | 1.00 | 1.49 | 0.54 | 2.51 | 0.92 | 1.26 |
| Between waves 2 and 3 | 1.79 | 4.57 | 0.83 | 1.34 | 0.87 | 2.00 | 0.78 | 1.11 |
| Between waves 3 and 4 | 1.79 | 3.71 | 0.72 | 1.26 | 1.02 | 2.52 | 0.84 | 1.30 |
| Between waves 4 and 5 | 3.86 | 13.66 | 0.67 | 1.12 | 1.25 | 3.31 | 0.79 | 1.46 |
| Between waves 1 and 5[c] | 2.12 | 7.32 | 0.82 | 1.33 | 0.84 | 2.41 | 0.84 | 1.24 |

[a] Seropositive men who experienced a CD4% decrease between waves 1 and 5 reported fewer AIDS diagnoses and/or deaths in their social networks than seropositive men who developed thrush and/or fever between waves 1 and 5 ($t=1.62$, df=1165, n.s.).

[b] Seropositive men reported more AIDS diagnoses and/or deaths in their social networks than did seronegative men ($t=0.9$, df=590, n.s.).

[c] Seropositive men reported more AIDS diagnoses and/or deaths in their social networks than did seronegative men ($t=5.4$, df=2141, $p<0.01$).

TABLE 3. Longitudinal Relationship of Stressful Life Events to CD4% Decrease and Development of Thrush and/or Fever in the Multicenter AIDS Cohort Study

| | Seropositive | | Seronegative | |
|---|---|---|---|---|
| Symptom and Stress | Odds Ratio | 95% Confidence Interval | Odds Ratio | 95% Confidence Interval |
| CD4% decrease of at least 25% | | | | |
| AIDS diagnoses and/or deaths in social network | 1.70 | 0.97–2.97 | 0.78 | 0.40–1.52 |
| Other serious stressors | 0.65 | 0.39–1.08 | 1.02 | 0.78–1.33 |
| Development of thrush and/or fever | | | | |
| AIDS diagnoses and/or deaths in social network | 0.95 | 0.78–1.16 | 1.00 | 0.72–1.39 |
| Other serious stressors | 0.89 | 0.73–1.07 | 0.81 | 0.64–1.04 |

with low statistical power. Consequently, results were pooled across all four wave-pairs. The fact that a 25% decrease in CD4% or the onset of thrush and/or fever in a given wave led to the exclusion of a subject from subsequent waves (table 1) means that the analysis of the pooled data is functionally equivalent to a discrete-time survival model with time-dependent covariates (15). Power was increased by the procedure of pooling the data across waves, although power to detect a two-fold increase in the odds of a drop in CD4% associated with exposure to stressful life events was still only 0.44 in the pooled data, compared with a power of 0.84 to detect a similar impact on the onset of thrush and/or fever. The results of the analysis of the drop in CD4%, therefore, must be interpreted with caution.

Parallel analyses were conducted among HIV-seronegative men to determine whether the observed patterns were unique to men infected with HIV. The comparatively large number of HIV-seronegative men in the cohort created acceptable statistical power for evaluating the effects of stressor events on both symptoms (0.91 for drop in CD4% and 0.79 for development of thrush and/or fever).

Table 3 presents summary results of the logistic regression analyses based on the pooled data. The effects of the control variables are not reported in this table, and the logistic regression coefficients associated with the stress measures have been exponentiated to create odds ratios. None of the stress odds ratios was meaningfully different from 1.0 in the group of HIV-seronegative men. None of the four odds ratios exceeded the bounds of the 95% confidence interval for the HIV-seropositive men. However, the odds ratio between AIDS diagnoses and/or deaths in the social network and subsequent drop in CD4% was fairly large in substantive terms among the HIV-seropositive men, and these stress and symptom variables are similar to those used by Coates et al. (unpublished 1989 study) in an analysis that documented a significant longitudinal association between stress and progression of HIV illness. It is conceivable that this represents a meaningful association that was not assessed powerfully in our sample.

As noted earlier in this paper, there are at least two substantive interpretations of an association between AIDS diagnoses and/or deaths and progression of HIV illness. The first interpretation, which was emphasized by Coates et al., is that major stressful experiences lower host resistance by affecting immune function. If this were the case, however, we would expect to see the same kind of effect for other major stresses, which we do not. It is noteworthy in this regard that analysis of the Multicenter AIDS Cohort Study data shows that AIDS diagnoses and/or deaths and other major stresses have similar effects on a screening scale of depression, suggesting that these two different sets of life events are experienced subjectively as being equally stressful. On the basis of this finding, we suspect that the first interpretation is incorrect.

The second interpretation is that exposure to AIDS diagnoses and/or deaths is associated with personal risk behaviors which cause the progression of illness and lead to a spurious association between this particular measure of stress and progression of illness. If the stress interpretation is the correct one, we would expect the odds ratios to be progressively larger as we go from AIDS diagnoses and/or deaths that occurred to acquaintances, friends, and lovers because the subjective sense of loss would increase with closeness. If, on the other hand, the second interpretation is the correct one, we would expect just the opposite pattern of results because early infection would be more strongly associated with the number of acquaintances and friends who died of AIDS death or were diagnosed as having AIDS than with number of lovers. The data are consistent with the second interpretation: for the HIV-seropositive men, the odds ratios between AIDS diagnoses and/or deaths of acquaintances, friends, and lovers were 3.00 (95% confidence interval=0.77–11.67), 1.77 (0.43–7.33), and 0.72 (0.24–2.09), respectively.

Additional analyses were carried out to determine whether the results for longitudinal relationships were robust. All models were estimated again with dichotomous versions of the stress measures (none versus one or more events) rather than the continuous measures used originally. A number of different weighing schemes were examined to evaluate the possibility that some of the events in the summary stress scales affected illness progression more powerfully than others. Interaction models were estimated to determine whether the associations were stronger in some wave-pairs than others. Analyses were carried out to determine whether the effects of stress occurred over a lag of 1 year rather than 6 months. Different cutoff points for a decrease in CD4% were investigated in the range of 20% to 40%. None of these analyses yielded evidence for an influence of stress on either decrease in CD4% or development of thrush and/or fever.

## DISCUSSION

It is important to realize that the analysis presented here has focused on a particular cohort at a particular time since exposure to HIV. We lack information on exactly when each of the HIV-seropositive men in the sample became infected, since each of them was seropositive at the time of the wave 1 data collection. We do know, however, that all of these men were still healthy in the summer of 1984, when the Multicenter AIDS Cohort Study subjects were assembled. There were other men who developed symptoms of HIV infection by that time and who presumably seroconverted at the same time as Multicenter AIDS Cohort Study participants. It is possible that exposure to serious stressor events played some part in the rapid onset of symptoms among those who had early onsets of illness. It is also possible that stress will come to play an important part in symptom onset in the Multicenter AIDS Cohort Study participants as we follow them over a longer period of time. For now, however, we are unable to detect any evidence that serious stressor events play a meaningful part in symptom onset among initially HIV-seropositive men in this cohort.

HIV-seropositive individuals and their health care providers can take some comfort in these results because they suggest that there is no need for asymptomatic people with HIV infection to restrict their lives in order to avoid exposure to stressful life experiences, nor a need to develop special skills for coping with stress in an effort to forestall the progression of HIV illness. The results also suggest that intervention programs designed to help people with HIV infection cope with stress are unlikely to be useful in prolonging health. This is not to suggest that such programs are unimportant. There is good evidence that HIV-seropositive people are under enormous stress (16) and that stress intervention programs can play an important part in improving their quality of life (2; unpublished 1988 paper by M.A. Fletcher et al.). The burden of maintaining physical health in the face of HIV infection, however, should not be seen as a goal or likely outcome of these programs.

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# The Psychiatrist's Role, Responses, and Responsibilities When a Patient Commits Suicide

Neil S. Kaye, M.D., and Stephen M. Soreff, M.D.

*The suicide of a patient is not an infrequent event in a psychiatrist's practice, and it has a major impact on the clinician as well as on the patient's family and the hospital staff. Dealing with a patient's suicide is a neglected topic in residency training, and many psychiatrists are never taught how to cope with such a situation. The authors review the relevant literature and draw on this as well as on their own clinical experience to recommend specific interventions. They point out that the psychiatrist has a leadership role and a number of responsibilities in the aftermath of a suicide, including notifying the family, the hospital staff, hospital officials, and patients who knew the deceased patient; meeting with the family, the staff, and the patients to encourage discussion and venting of feelings; attending the funeral; and accurately documenting events in the medical record. The psychiatrist should also attend to his or her own needs by seeking support from a colleague and should ensure that a psychological autopsy is performed in order to facilitate learning, improve care of patients in the future, and help bring about closure for the psychiatrist so that the quality of his or her care of other patients is not compromised.*

(Am J Psychiatry 1991; 148:739–743)

Suicide stands as a most powerful, indelible event. The thought of a patient making a successful suicide attempt continues to strike fear in the hearts of physicians despite years of training and research (1–3). However, if a psychiatrist is in practice long enough, it is reasonably likely that he or she will have a patient who commits suicide. Chemtob et al. (4) reported that in their national survey, 51% of the responding psychiatrists had had a patient who committed suicide. Patients with affective disorders have a suicide rate of 15%, and those with schizophrenia have a suicide rate of 10% (5). In spite of the frequency of this event, it remains difficult to discuss.

A patient's suicide can be more devastating when it occurs while the psychiatrist is in training (6, 7). Brown (6) found that 33% of the psychiatric residents in his study had had a patient who committed suicide. He noted the residents' vulnerabilities during training, and he found that among those who had experienced a patient's suicide, 77% felt that the impact was "severe" or "strong," and 62% felt that it had a "major effect" on their development. Yet, rarely are residents specifically taught how to handle a suicide. Mentors infrequently discuss their own experiences in this area.

Perhaps it is even more devastating when the doctor-to-be experiences such an event while in medical school. Krueger (8) discussed the impact of a suicide on a medical student and his colleagues, as well as ways of dealing with its repercussions.

Lindemann (9), Caplan (10), and Silverman (11) emphasized aid to the survivors in situations where death has occurred. They based their interventions partly on the premise that bereaved persons have a higher risk of morbidity and mortality than those who have not experienced such a loss. Ness and Pfeffer (12) found that the survivors of individuals who commit suicide are particularly in jeopardy. These families sustain a great sense of shock, engage in a protracted search for an explanation, have difficulty in talking about the loss, show prolonged feelings of guilt, and become very isolated. Additionally, the family members themselves are at greater risk of suicide.

Shneidman (13) coined the term "postvention" to describe activities that serve to reduce the aftereffects of a traumatic event. He emphasized the importance of psychiatric intervention after a suicide. Still, there remains little in the literature to guide physicians in their conduct during this highly stressful time (3, 14–16). This paucity of information on procedure and protocol can prove particularly unfortunate as the psychiatrist and the other survivors wrestle with feelings of shock and anger, the search for an explanation, and a sense of guilt (12).

This article offers guidelines and recommendations to the psychiatrist especially and to any psychotherapist who sustains the loss of a patient by suicide. Both of us

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have treated patients who committed suicide during or shortly after our psychiatric residencies. Using experience gained in managing these cases, we outline some useful steps in managing the complex issues that emerge. Although each patient, situation, and clinician is unique, certain universal questions, issues, and events arise.

It is important to emphasize that a patient's suicide is a very personal event. Although many suicides will share themes, it is critical to be sensitive to the nuances of a case and to choose the appropriate postventions accordingly. We have organized these into five categories: the family, the staff, other patients, the psychiatrist, and risk management. Many of the postventions will take place simultaneously. Nonetheless, the categories we have chosen provide a useful framework in which to conceptualize them.

## THE FAMILY

The psychiatrist should contact the family as soon as possible. Whenever feasible, the contact should be in person and be in a quiet and private setting. The family should be allowed as much time as they need to ask questions and to begin grieving. If the psychiatrist is open with feelings about the event and the loss, the sharing may help them to discuss their own feelings.

It is important to tell the family realistically that all that could have been done for the patient was done. For example, it is a consolation to the survivors that the paramedics acted "valiantly" and the trauma center used "heroic efforts" in attempts to save the patient. It is also important to tell them of all the efforts to treat the patient before the suicide.

Each family member will respond uniquely to the death. Sometimes the family members seem to be in a hurry and to want to end the discussion quickly. When this happens, there is often value in helping them to talk about their reactions. At other times the family may be quite open and emotional, and just the presence of the psychiatrist is enough for the first meeting. They must be met "where they are," yet the psychiatrist can set an example by creating an atmosphere in which everything can be discussed and they are given "permission" to grieve and to feel pain, sadness, anguish, and anger.

A particularly useful question to explore with the family is whether they had any feelings that the patient would attempt and/or eventually succeed in committing suicide. Sometimes family members will say they "felt" that the therapist was going to tell them about the suicide even before he or she told them anything. Families also sometimes "knew" from what the patient had said and done in the past that there might be a fatal outcome.

Before ending the first meeting, the psychiatrist should let the family know how he or she can be reached and inquire about their expectations of help in the immediate future. These might include setting up another meeting and discussions about wakes, funerals, memorials, donations, and cards.

The family will usually guide the therapist concerning the appropriate duration of contact, but we suggest that contact should be maintained at least through the funeral and until the autopsy results are available. Psychiatric referrals are often indicated.

Involving the clergy at once is perhaps one of the most productive interventions. They are skilled in these matters and can provide essential support. Religion can provide answers that medicine/science cannot.

A natural death is often painful and difficult for a family to deal with, but a suicide can be extremely difficult, devastating, and overwhelming for the survivors. An important part of the psychiatrist's job is to acknowledge to the family that the grieving process may be much harder, more complex, and more painful than it is for other deaths (12). "The survivor victims of suicidal death are saddled with an unhealthy complex of emotions: shame, guilt, anger, perplexity" (13).

Encouraging the family to ask the local media to respect their privacy and grief is often a successful maneuver. Most newspapers will not run an obituary twice. Therefore, if the family supplies the obituary, the newspaper is far less likely to write a more explicit version.

The family often awaits the autopsy with the same anxieties as does the psychiatrist. It may be helpful to meet with the family to discuss the autopsy report. The psychiatrist's availability, if only to interpret the medical jargon, will usually be appreciated.

## THE STAFF

The psychiatrist has an important responsibility to inform the hospital staff of the death as soon as possible and help them deal with their feelings. In an inpatient unit, one of the most difficult tasks is notifying three shifts of staff members about the death. The technique is not unlike that used with the family. The members of the current shift and other available staff members should be gathered together and told as a group. It is also important to instruct this shift how the remaining shifts are to be notified. The psychiatrist should avoid casting blame and allow for group support and venting of emotions. Hodgkinson (16) has depicted the staff's bereavement and underscored the benefit to them of organizational structural support. They should be made aware of the agenda for dealing with the death (the time of the funeral, memorial service, etc.) when this information is available.

There are a number of benefits for the staff in attending the funeral and memorial services. Markowitz (17) has described these. Our experience is that families will not only accept staff members but welcome them. In one of our cases, the social worker who went to the funeral not only demonstrated the hospital's concern for the family and was well appreciated by them but was also able to share with the treatment team how the family was doing and how they handled the funeral. The psychiatrist who attended the funeral (N.S.K.) felt welcomed and had the pleasure of learning more by hearing others talk about the patient.

The eulogy may introduce facets of the patient and his or her life about which the therapist was unaware; so may stories told by relatives and friends. It is sad but often true that one may come to know a person better at the funeral than one did during his or her life.

Cards may be sent and donations made on a personal basis. In one of our cases, the family asked for all donations to be made to a local mental health outreach center. These gestures were warmly received by everyone and assured the staff that their efforts were appreciated.

The reason a person takes his or her own life is a very private matter. Commonly, and often quite privately, staff members will review every aspect of their own and each others' interactions and actions prior to the suicide. It is our experience that rarely has someone done something that specifically resulted in the suicide. Nonetheless, some staff members will feel personally responsible for the actions of the patient. This requires group support and processing and may take multiple meetings to understand. In one of our cases, the process of closure and healing was not completed until after a grand rounds presentation dealing with the issue 1 year later.

We strongly support the use of a psychological autopsy as described by Litman et al. (18). A respected psychiatrist who is unfamiliar with the case should preside, and notes should be kept. There are two clear purposes of the psychological autopsy. The first is as a cleansing exercise to allow all feelings to be aired openly. The second is to allow for policy reform, for learning to take place, and for better patient care (19). Many institutions have a format for conducting a psychological autopsy as part of their policies and procedures manual. We encourage those that do not to develop such a format.

The staff must also move on, so that the living patients do not feel abandoned. Over time, the acuteness of the feelings will be tempered, and both staff and patients will resume their previous routines.

## OTHER PATIENTS

A rapid, organized meeting of all patients with the staff is crucial. The presence of the psychiatrist is imperative. Patients will have many feelings, but especially important is their concern for the ability of the staff to help them, since in their eyes the staff may have been unable to save the deceased. Hodgkinson (16) pointed out the increased vulnerabilities of the other patients when a patient commits suicide. They may not only be overwhelmed by a host of intense feelings but also be at some risk of acting on their own suicidal desires and impulses. In fact, Cotton et al. (20) suggested canceling passes for the first few days after a suicide.

Setting the stage by having both staff and patients share feelings is important and reinforces the sense of community of the inpatient ward. It is equally important to have them recognize the positive and negative aspects of the deceased—what they liked and disliked about the person. Patients may see the staff as weaker as a result of the suicide, and this also needs to be recognized. Decisions to keep the ward locked for an added feeling of security or to limit passes will need to be addressed. If the person who committed suicide was an outpatient but was involved in a group, the procedures are much the same as for an inpatient setting. In this case, however, it is likely that the members will have heard of the death from the media or from one another before the group convenes. It is important to make this the first topic of discussion at the next group session.

In the following days, patients may try to comfort the staff in the group or alone. It is important to note and to explore the feelings and thoughts behind such efforts. Similarly, some patients may intentionally try to devalue the staff by continually reminding them of their "failure." These efforts can stir negative countertransference feelings that must be acknowledged and should be discussed in supervision.

## THE PSYCHIATRIST

How and when a psychiatrist finds out about a patient's suicide influences the response. It will inevitably require interrupting other plans. If the patient was associated with a hospital or other facility, it is important to notify the administration promptly.

The next thing to do is get some support for oneself. The psychiatrist should take the time to contact a trusted colleague or mentor, preferably someone with experience in this area. It is likely that this person will have been through such an experience in his or her career, even though others may not be aware of it. A small amount of time should be taken to review the case and to reflect on the questions that come to mind about the patient and about the treatment.

The obvious thought of "where did I go wrong?" need not be pursued at this time, but at least it should be acknowledged that the thought exists. It is helpful to figure out the order in which things will need to be done and to make a list to help keep track. In both of our cases, the support, direction, and advice of senior attending psychiatrists proved invaluable in getting us through the night and the next few days. Ness and Pfeffer (12) pointed out, "With striking unanimity therapists have said that formal and informal consultation with colleagues is one of the most important and helpful actions to take in coping with a patient's suicide."The psychiatrist should consider attending the wake and/or funeral; the benefits are many. Most importantly, we feel that grieving needs to be done, at least initially, in a group setting. This is the basis of the Jewish "sitting Shiva" and the Christian wake. In our experience, fears that people will look askance at the psychiatrist who attends and hold him or her responsible for the death have proved to be unfounded. Cards and donations are appropriate in most cases. As we have mentioned, the family will often embrace the idea that these can be targeted to help others with mental or emotional problems. "Contrary to popular belief, a statement that 'I'm sorry this happened' is not an admission of responsibility and often soothes hurt feelings" (21).

The psychiatrist must be available for the staff and share honestly and openly thoughts and feelings about the situation. Being on time at rounds and meetings is critical. The psychiatrist's behavior will be interpreted by the staff, and it must coincide with his or her words. It is important to remember that one has a place on the team as both a member and the leader; the others will follow the lead. The staff needs to know that the psychiatrist is concerned for their welfare.

Attending the autopsy is an individual choice, but it is not taboo. Psychiatrists are physicians. If the cause of death is equivocal, cooperation with the pathologist can help him or her decide this crucial issue. In some cases, particularly neuropsychiatric ones, the psychiatrist may have important information to share and also to learn.

A psychological autopsy should always be conducted. Both of us have taken part in them, as participants and as leaders, and can attest to their usefulness in laying the case to rest. The atmosphere should be that of a supportive review. The focus should be less on "what did we do wrong?" and more on what can be learned from this and what can be done better.

An investigation will undoubtedly be conducted. Legal counsel should be consulted before any statements are given. It is the psychiatrist's right to have counsel present at any and all questioning, and depending on the case and the likelihood of a suit, this may be warranted. We suggest being conservative and involving counsel at all stages.

Billing the family for past services rendered is often a difficult task. Nonetheless, it is usually the correct approach. To do otherwise might imply guilt (21). Fauman (22) pointed out that most patients and their families equate outcome with the quality of the treatment. However, physicians cannot guarantee an outcome, whether it be in psychiatry, surgery, or medicine. They bill for their time and their knowledge.

Moving on is important. Experiencing a patient's suicide will create a lasting memory. The experience should be shared with younger clinicians, particularly those still in training. Only through personal contact with a caring mentor can the delicate issue of a patient's suicide be addressed.

## RISK MANAGEMENT

Most institutions have risk management officers whose job is to manage the problem for the hospital. Therefore, they will have the hospital's and not the psychiatrist's interest at heart. It is important to cooperate with them, but being cautious is not unreasonable, and consulting an attorney may be a good idea. Also, the laws of each state reflect to what degree the psychiatrist may be liable if a tort action should arise.

Risk management can help by controlling the media and keeping them away, so that the psychiatrist can perform the various functions we have noted and tend to his or her other patients as well. For the psychiatrist as an individual, notifying the malpractice insurance carrier may be part of managing the risk. However, we feel this should not be done without first obtaining legal counsel; often it will depend on the practice setting.

It is important to complete the medical record. Notes that are entered should be dated accurately, and it should be made clear that they are written after the death. One should not apologize in a note or attempt to reason or justify decisions in retrospect. If the documentation and reasoning have previously been satisfactory, there is little to fear. The event should be described, with the facts given as they are understood to have occurred, and drawing conclusions should be avoided.

## CONCLUSIONS

Patients who commit suicide remind us how impotent we sometimes are in our efforts to help (2, 17, 23). However, if a suicide does occur, the treating psychiatrist has a role and a number of responsibilities and responses. He or she has a leadership position with respect to the family and the staff and has the responsibility of informing the family, working with the staff, communicating with the proper officials, and accurately documenting events in the record.

As a treater, as a clinician, and as a person, the psychiatrist has a number of individual responses to the event and to the loss and also has the additional responsibility of obtaining support. It is particularly difficult for a physician in this position to seek out the supervision and assistance of a more experienced colleague. Nonetheless, this can be invaluable in dealing with the aftermath of a patient's suicide, allowing the psychiatrist to learn from the death to be better prepared in the future.

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## New Policy for References

Effective with the September 1991 issue, *The American Journal of Psychiatry* will institute a policy of listing the names of all authors of work cited in references. Authors of submitted manuscripts and letters to the Editor must include the surnames and initials of all authors in references. The use of "et al." is no longer acceptable.

# The Negligible Effects of California's 1982 Reform of the Insanity Defense Test

Margaret A. McGreevy, M.A., Henry J. Steadman, Ph.D.,
and Lisa A. Callahan, Ph.D.

Objective: *The authors' goal was to determine whether changing the insanity test in California in 1982 actually affected use of the insanity defense.* Method: *They gathered information on all individuals who entered the insanity plea (N=1,300) and all those acquitted by reason of insanity (N=665) in seven counties in California 3 years before and 3 years after the change in the test of insanity. They focused on whether California's revision of the insanity test affected the number and rate of insanity pleas, the number and rate of insanity acquittals, the characteristics of individuals using the defense, the target offenses, and the length of stay of insanity acquittees.* Results: *The reform did not affect the rate of insanity pleas or acquittals, the characteristics of those using the defense, or their length of confinement.* Conclusions: *Although the reform had no direct effects on the use of the insanity defense, the authors hypothesize that an indirect change in criminal sentencing practices led to a decrease in the number and rate of insanity pleas and acquittals.*

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In June 1982, a jury returned a verdict of not guilty by reason of insanity in the case of John Hinckley, who had been tried for his attempt to assassinate then-President Ronald Reagan. This verdict generated pervasive calls for reform of the insanity defense throughout the United States. Congress immediately held hearings on the insanity defense and passed the Insanity Defense Reform Act in 1984. In the 3 years following Hinckley's acquittal, 34 states enacted limitations and/or reforms in their insanity defense statutes (1). The reforms included changes in the burden and standard of proof, changes in commitment and release procedures, enactment of guilty but mentally ill laws, and changes in the test of insanity. In this paper we examine the impact of one of those reforms—California's 1982 change in the test of insanity—to determine its effect on the use of the insanity defense.

Several tests of insanity have been used in the United States since the mid-1800s, when the McNaghten standard—commonly referred to as the "cognitive" or "right-wrong" test—was adopted in most U.S. courts. The McNaghten test states that a person is not held criminally responsible if at the time of the offense "he/she was laboring under such a defect of reason as not to know the nature and quality of the act he/she was doing or did not know the action was wrong." It was used alone or in conjunction with the "volition" or "irresistible impulse" standard, which refers to the defendant's loss of ability to avoid doing the act in question, until 1962, when the American Law Institute (ALI) standard was drafted. The ALI standard was then widely accepted in the states.

In 1954, the Durham test was adopted in the District of Columbia. It was seen as reflecting growing advances in the field of psychiatry and as broadening the range of individuals able to use the insanity plea. It states simply that an accused person is not criminally responsible if the unlawful act was the product of mental disease or defect. Although it was widely heralded by the psychiatric community, it did not win acceptance in the state courts and was replaced in 1972 by the ALI standard in the District of Columbia.

The jury in the Hinckley trial used the ALI test, which states that a person is not responsible for criminal conduct if "at the time of such conduct, as a result of mental disease or defect, he/she lacks substantial capacity either to appreciate the criminality (wrongfulness) of his/her conduct or to conform his/her conduct to the requirements of the law." It combines the cognitive aspect of the McNaghten standard and the volition emphasis of the irresistible impulse test. For many, it was seen as a compromise with previously used tests that were considered either too narrow (McNaghten) or too broad (Durham) (2).

Research on the effect of the insanity test on the use

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of the insanity defense is quite limited. The available data from five states that changed their insanity tests are not conclusive as to whether the changes affected the use of the insanity defense (3). In all five states studied, the McNaghten standard was replaced by a seemingly more liberal ALI or Durham standard. Studies of insanity acquittals in the District of Columbia following the 1954 change from the McNaghten rule plus an irresistible impulse standard to the less restrictive Durham test (4–6) found an increase in the percentage of defendants who were acquitted by reason of insanity (from 0.5% to 2.5%) over a 6-year period (1954 to 1959). Similarly, data from Maryland (7) and Oregon (8) and findings from earlier work in California (9) suggest that the absolute number of insanity pleas or acquittals rose after these states changed from the McNaghten to the ALI standard. In Maryland, 8% of the male felons evaluated for mental illness were found to be not responsible in 1966, but in 1973, 6 years after the change to the ALI test in 1967, 19% were so determined (7). In the 6 years before Oregon's change from McNaghten to ALI (1966–1971), 44 defendants were acquitted as not guilty by reason of insanity, compared with 734 defendants during 1972–1982 (8). In California, the number of insanity acquittals rose sharply in the year following the switch to the ALI standard, from 187 acquittals in 1978 to 270 in 1979 (9).

In contrast, Pasewark et al. (10), who conducted a more in-depth study of Wyoming's change in the test of insanity, found no significant impact on the rate of insanity pleas or acquittals or in the characteristics of defendants using the defense following a change from the McNaghten rule plus an irresistible impulse standard to the ALI standard and a change in the type of trial conducted from bifurcated to single-faceted.

Results from two related areas of research also address the insanity test issue. A 2-year, prospective study of forensic evaluations in which the evaluating psychiatrists were asked to indicate whether the defendant evaluated for nonresponsibility met cognitive and/or volitional criteria (11) supported the argument that the insanity test used affects the number and composition of those invoking the insanity defense. The research found that nearly one-quarter (24.4%) of those evaluated as nonresponsible met only a volitional criterion. They also found high correlations (0.94 and 0.86) among the three cognitive standards used. These finding suggest that a test incorporating both cognitive and volitional criteria would be broader and therefore may result in a higher plea rate than would a test with only a cognitive aspect.

Studies using mock juries suggest that jurors understand their roles and responsibilities in insanity trials and make decisions consistent with the law. In a mock jury trial involving incest, Simon and Aaronson (12, 13) found that juries rendered more insanity acquittals when instructions consistent with the Durham test or when no instructions were given than when they were instructed according to the McNaghten test, but other studies have not duplicated these results. Finkel and Handel (14) found no significant differences in the verdicts of mock juries instructed according to six different tests.

The cited studies on the effects of changing the test of insanity are limited in both their scope and methodology. The studies suggesting that the number of insanity acquittals increased following a switch from the McNaghten test to either the Durham rule or the ALI standard looked only at the number of insanity acquittals and did not take into account trends across time or examine volume of insanity pleas or felony indictments (3, 7). Although the forensic evaluation has been found to be a strong predictor of insanity adjudication (15), other factors related to the judicial process may influence a not guilty by reason of insanity acquittal. Studies based on the verdicts of mock juries are limited in that the vast majority of insanity cases do not go to juries. Rather, they are settled by plea bargaining or with a bench trial. Finally, the work of Pasewark et al. (10), which was a direct study of the effect of changing the test of insanity, indicated that the changes had no significant effect on the use of the insanity defense. The statutory changes they studied took place in a state where there was little use of the defense, and it could be argued that a change from the McNaghten rule plus an irresistible impulse clause to an ALI standard is relatively minor in that both contain a cognitive aspect and a volitional aspect. The major difference in the two standards of the insanity defense used in Wyoming was in the level of cognitive impairment required.

The research reported in this paper expands on previous work in that both plea and acquittal data from a populous state (California) are used to examine what happened when the insanity test was changed. Specifically, we studied California's July 1982 revision of the test of insanity from the ALI test to a modified McNaghten test. The revision also eliminated the defense of diminished capacity. The McNaghten test of insanity was used in California from the early 1900s until it was replaced in September 1978 by the ALI test. In 1982, as part of Proposition 8, the ALI standard was replaced by a modified McNaghten standard in which a conjunctive "and" replaced the disjunctive "or" used in the traditional McNaghten test. This reform was generally seen as an attempt to make the insanity defense more restrictive. In 1984, the California Court of Appeals ruled that the 1982 state law should be seen as simply returning California to the McNaghten test rather than creating a new insanity test (16).

In this paper we focus on whether California's revision of its insanity test affected the number of insanity pleas and acquittals, the rate of insanity pleas and acquittals, the percentage of successful pleas, the characteristics of individuals using the defense, and the length of stay in psychiatric facilities of insanity acquittees. To assess the impact, data on all individuals entering the insanity plea during a 6-year period, 3 years before the reform (July 1979 to June 1982) and 3 years after the reform (July 1982 to June 1985), were gathered in seven counties. Our conclusion, consistent with the findings of Pasewark et al. (10) in Wyoming, is that changing the test had little effect on the use of the insanity defense in California.

## METHOD

Our data in California were collected as part of an eight-state study of insanity defense reform. During 1987, county criminal court dockets in six counties (Alameda, Orange, Sacramento, San Diego, San Francisco, and Santa Clara) and five representative districts of Los Angeles county (Central, Compton, Long Beach, Santa Monica, and Van Nuys) were searched to identify all individuals raising the insanity plea from July 1979 through June 1985. These counties were selected because, together, they produced about two-thirds of the insanity acquittals in the state. Our sample included 1,300 insanity pleas and 665 not guilty by reason of insanity acquittals from the seven counties over 6 years. A defendant was included in the study if an insanity plea was raised at any time before his or her adjudication. Once all insanity pleas were identified, information on the target offenses, previous (known) mental health and criminal justice histories, adjudication, and disposition were obtained from court case files and records maintained by the California Department of Mental Health and the California Department of Corrections.

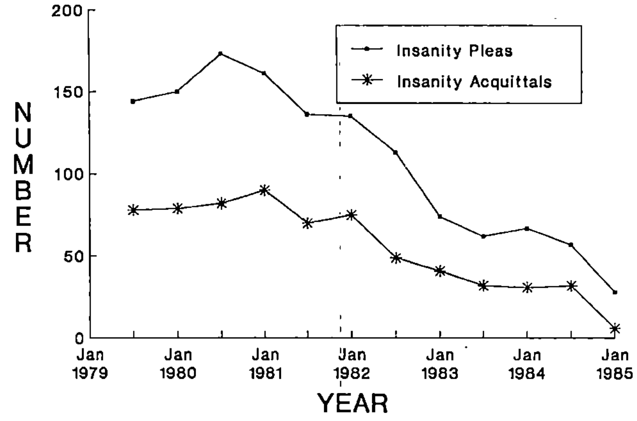
A time series analysis in a multiple regression equation was used to assess the effects of the 1982 reform on the plea and acquittal rates. A dummy variable was used to represent before reform (rated 0) or after reform (rated 1). It represented changes in the intercept (level) of the rate before to the rate after reform. A second variable was coded to represent a linear term of time in which decreasing negative units (i.e., $-5.5$ to $-0.5$) represented the before-reform period and increasing positive units (0.5 to 5.5) represented the after-reform period (17). A third variable represented the interaction between these two variables, which reflects changes in the slope of the line before reform to after reform. An F test measuring the contribution to $R^2$ made by both the slope and intercept variables was used to determine whether there was a significant reform effect. The equation for the model was

$$\text{Biannual Rate} = \text{B0} + \text{B1(reform)} + \text{B2(time)}$$

$$+ \text{B3(reform} \times \text{time)}.$$

Chi-square analyses were conducted on the characteristics of the individuals entering insanity pleas and those acquitted before and after reform as well as for the target offenses and the lengths of stay to determine whether there were significant differences before and after reform.

**FIGURE 1. Number of Insanity Pleas and Acquittals in California Before and After 1982 Reform of Insanity Test**[a]



[a]The before-reform period includes the cases of all individuals indicted on or before June 30, 1982, and the after-reform period includes all indicted on or after July 1, 1982.

## FINDINGS

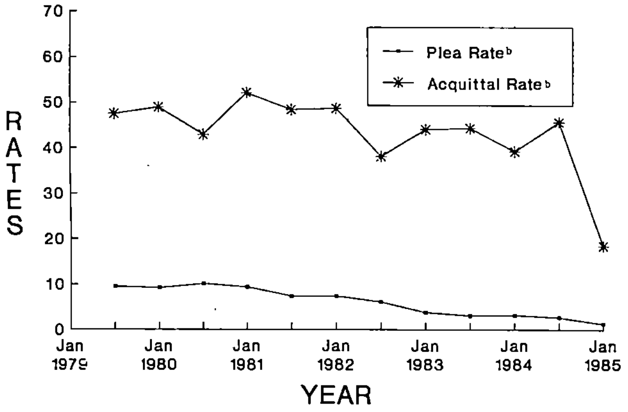
### *Volume of Insanity Cases*

The number of insanity pleas and acquittals in the study counties are shown by 6-month intervals, starting with July 1979, in figure 1. The number of insanity pleas rose briefly in the first year of the before-reform period to a high of 173 in the last half of 1980 but then began a sharp, steady decline to a low of 28 in the first half of 1985. The number of acquittals followed a similar course but ranged from a high of 90 in 1981 to a low of 6 in the first half of 1985. There was a slow but steady rise in felony indictments (not shown) during the same period from approximately 15,000 indictments in the last half of 1979 to 22,500 in the first half of 1985.

Figure 2 presents the plea rate (pleas per 1,000 felony indictments) and the acquittal rate (acquittals per 100 pleas) in the seven study counties. The plea rate reflects use of the insanity plea in a broader context than the absolute number shown in figure 1 because it is based on the number of felony indictments and, in effect, controls for fluctuations in crime. The acquittal rate represents the percentage of insanity pleas that actually resulted in insanity acquittals. The plea rate dropped from 10 per 1,000 indictments before 1981 to just over one per 1,000 indictments in 1985. The acquittal rate remained relatively stable at around 40% throughout the study period with the exception of the first half of 1985, when it dropped dramatically. Whether this was simply an aberration or was indicative of a changing trend cannot be determined from our data. A visual examination of these data strongly indicates that the plea rate was already on the decline before the 1982 reform and that the reform did not have a major impact on the direction or rate of decline.

To test for the statistical significance of the observed

**FIGURE 2. Insanity Plea and Acquittal Rates Before and After 1982 Reform of Insanity Test[a] in California**



[a] The before-reform period includes the cases of all individuals indicted on or before June 30, 1982, and the after-reform period includes all indicted on or after July 1, 1982.

[b] The plea rate is the number of pleas per 1,000 felony indictments, and the acquittal rate is the number of insanity acquittals per 100 insanity pleas.

trends, an F test was used for the combined effect of the slope and intercept variables on the plea rate and the acquittal rate. The results, given in table 1, indicate that the introduction of the revised insanity test in California in 1982 simply continued trends that were already underway.

### *Characteristics of Individuals Using the Insanity Defense*

Table 2 presents the sociodemographic characteristics, previous mental health and criminal justice involvement, and diagnoses of all individuals raising the insanity defense and those acquitted by reason of insanity before and after reform in the seven study counties. Clearly, there were no significant changes before and after reform in the characteristics of individuals entering insanity pleas or those acquitted. The diagnosis of schizophrenia was the only variable with a statistically significant change after reform: fewer of those acquitted were diagnosed as schizophrenic after the reform than before the reform (table 2). Interestingly, the decline in diagnoses of schizophrenia was almost entirely offset by a rise in the category of major mental illness other than schizophrenia (other psychoses or affective disorders).

We also compared individuals who unsuccessfully pled insanity with those who were acquitted and found a significant difference in diagnosis ($\chi^2=207$, df=6, $p<0.0003$). Those acquitted were more likely than those who entered unsuccessful pleas to be diagnosed as having schizophrenia or other major mental illness. A larger percentage of individuals who pled insanity unsuccessfully than those acquitted were diagnosed as having personality disorders, substance abuse, or no mental illness.

**TABLE 1. Multiple Regression Analyses Assessing Change in Rates of Insanity Pleas and Acquittals in California Due to 1982 Reform of Insanity Test[a]**

| Variable | Value |
|---|---|
| Plea rate[b] | |
| Level | |
| Before reform | 7.4 |
| Change | −1.7 |
| After reform | 5.7 |
| Slope | |
| Before reform | −0.5 |
| Change | −0.3 |
| After reform | −0.8 |
| Acquittal rate[b] | |
| Level | |
| Before reform | 49.28 |
| Change | −2.42 |
| After reform | 46.86 |
| Slope | |
| Before reform | 0.40 |
| Change | −3.22 |
| After reform | −2.82 |

[a] Nonsignificant results from tests of the combined effect of the slope and intercept variables for plea rate ($F=2.58$, df=2, $p<0.14$) and acquittal rate ($F=0.91$, df=2, $p<0.44$).

[b] The plea rate is the number of pleas per 1,000 felony indictments, and the acquittal rate is the number of acquittals per 100 insanity pleas.

### *Target Offense*

The most serious criminal charges for those who entered an insanity plea and those who were acquitted by reason of insanity are also shown in table 2. No significant differences were found between before and after reform in the crime categories of either group. It is clear, however, that the majority of those who pled insanity and those who were acquitted were charged with violent offenses. Approximately two-thirds of the defendants pleading insanity were charged with murder, physical assault, or other violent offenses, and three-fourths of those acquitted were so charged. A comparison of the target offense of successful and unsuccessful insanity pleas indicated that insanity defendants charged with violent offenses were significantly more likely to be found not guilty by reason of insanity than those charged with burglary, property damage, or other minor offenses ($\chi^2=61$, df=2, $p<0.001$).

### *Length of Stay*

The numbers of individuals acquitted by reason of insanity who were hospitalized at acquittal and were still hospitalized 1, 2, and 3 years after their acquittal are shown in table 3. No significant differences were found in the percentage of acquittees hospitalized at acquittal or at the yearly intervals before versus after reform. The median length of stay for those who were acquitted before the reform was 1,326 days; it was 1,404 days for those who were acquitted after the reform.

**TABLE 2. Characteristics of Individuals Pleading Insanity and Those Acquitted by Reason of Insanity Before and After 1982 Reform of Insanity Test in California**

| | Pleas | | | | Acquittals | | | |
|---|---|---|---|---|---|---|---|---|
| | Before Reform | | After Reform | | Before Reform | | After Reform | |
| Characteristic | N | % | N | % | N | % | N | % |
| Sex | | | | | | | | |
| Male | 802 | 90.8 | 362 | 90.5 | 419 | 89.0 | 168 | 88.4 |
| Female | 81 | 9.2 | 38 | 9.5 | 52 | 11.0 | 22 | 11.6 |
| Ethnicity | | | | | | | | |
| White | 451 | 53.3 | 212 | 55.1 | 263 | 63.8 | 105 | 66.9 |
| Minority | 395 | 46.7 | 173 | 44.9 | 149 | 36.2 | 52 | 33.1 |
| Education | | | | | | | | |
| Less than high school | 260 | 41.3 | 106 | 37.6 | 110 | 38.1 | 33 | 31.1 |
| High school or more | 370 | 58.7 | 176 | 62.4 | 179 | 61.9 | 73 | 68.9 |
| Marital status | | | | | | | | |
| Single | 482 | 60.9 | 212 | 57.5 | 275 | 64.1 | 112 | 62.2 |
| Separated or divorced | 123 | 15.5 | 58 | 15.7 | 48 | 11.2 | 21 | 11.7 |
| Married | 186 | 23.5 | 99 | 26.8 | 106 | 24.7 | 47 | 26.1 |
| Previous history | | | | | | | | |
| No psychiatric hospitalization | 209 | 29.7 | 95 | 29.1 | 69 | 19.1 | 27 | 18.9 |
| Psychiatric hospitalization | 495 | 70.3 | 232 | 70.9 | 292 | 80.9 | 116 | 81.1 |
| No arrests | 162 | 24.4 | 79 | 25.5 | 86 | 28.1 | 32 | 27.6 |
| Arrests | 501 | 75.6 | 231 | 74.5 | 220 | 71.9 | 84 | 72.4 |
| Diagnosis | | | | | | | | |
| Schizophrenia[a] | 436 | 54.9 | 185 | 51.0 | 308 | 67.2 | 117 | 62.2 |
| Affective disorder or other psychosis | 111 | 14.0 | 70 | 19.3 | 75 | 16.4 | 44 | 23.4 |
| Developmental disabilities | 30 | 3.8 | 17 | 4.7 | 14 | 3.1 | 8 | 4.3 |
| Personality disorder | 78 | 9.8 | 40 | 11.0 | 14 | 3.1 | 2 | 1.1 |
| Substance abuse | 45 | 5.7 | 16 | 4.4 | 13 | 2.8 | 7 | 3.7 |
| Other mental illness | 57 | 7.2 | 18 | 5.0 | 34 | 7.4 | 8 | 4.3 |
| No mental illness | 37 | 4.7 | 17 | 4.7 | 0 | 0.0 | 2 | 1.1 |
| Crime category | | | | | | | | |
| Murder | 155 | 17.6 | 71 | 17.8 | 83 | 17.7 | 35 | 18.3 |
| Physical assault | 335 | 38.1 | 151 | 37.8 | 207 | 44.0 | 89 | 46.6 |
| Other violent crime | 88 | 10.0 | 41 | 10.3 | 59 | 12.6 | 25 | 13.1 |
| Robbery | 111 | 12.6 | 44 | 10.0 | 43 | 9.1 | 20 | 10.5 |
| Property crime | 113 | 12.9 | 42 | 10.5 | 50 | 10.6 | 11 | 5.8 |
| Other minor crime | 77 | 8.8 | 50 | 12.5 | 28 | 6.0 | 11 | 5.8 |

[a] Significantly fewer of those acquitted were diagnosed as having schizophrenia after reform than before ($\chi^2=14$, df=6, $p<0.05$).

**TABLE 3. Hospitalization Rate at and After Acquittal of Individuals Found Not Guilty by Reason of Insanity Before and After 1982 Reform of Insanity Test in California**

| | Before Reform (N=445) | | After Reform (N=184) | |
|---|---|---|---|---|
| Status | N | % | N | % |
| Hospitalized at acquittal | 417 | 93.7 | 177 | 96.2 |
| Still hospitalized 1 year after acquittal | 374 | 84.0 | 160 | 87.0 |
| Still hospitalized 2 years after acquittal | 322 | 72.4 | 138 | 75.0 |
| Still hospitalized 3 years after acquittal | 255 | 57.3 | 108 | 58.7 |

## DISCUSSION

The findings reported here represent a comprehensive demonstration that changing the test of insanity has no significant impact on the use of the insanity defense in practice. Despite an increase in felony indictments, the number of insanity pleas and acquittals were clearly on the decline in California before 1982, when the voters endorsed a more restrictive version of the insanity test. Our data indicate that changing the test had little effect on the percentage of individuals raising the defense (plea rate) or on those who were acquitted (acquittal rate). Furthermore, neither the characteristics of individuals using the defense nor the crimes for which they were acquitted showed any significant change after versus before reform.

Our findings add substantial weight to the work of Pasewark et al. in Wyoming, who found no significant effects of changes in that state's insanity test. Before our current study, the work of Pasewark et al. was the only one that was based on both plea and acquittal data for a substantial period of time before and after reform. The studies that documented a rise in insanity acquittals following a change in the insanity test relied only on the number of acquittals and had very limited longitudinal data before and after the reforms.

Although it is apparent that changing the test in California in 1982 did not have an impact on the use of the insanity defense, our findings suggest that something may have affected its use during 1980. In the latter half of that year the number of insanity pleas began to drop and then steadily declined at least through 1985, when we completed our selection of sample cases. Insanity acquittals started to decline in 1981, shortly after the decline in insanity pleas. A potential explanation for these declines is that they were the indirect result of changes in commitment practices brought about by the introduction of determinate sentencing in California.

In 1977, California adopted determinate sentencing for individuals convicted of crimes. In 1978, the California Supreme Court found that "equal protection precluded individuals committed to state institutions following acquittal of criminal offenses on grounds of insanity from being retained in institutional confinement beyond maximum term of punishment for underlying offense" (18). Thus, in September 1979 the California legislature set forth a maximum term of commitment for those acquitted by reason of insanity that equaled the longest term of imprisonment which could have been imposed for the offense, disregarding any "good-time" credit applicable to those convicted. Since good-time credit, which can be up to 50% of the sentence, was not included in the maximum term of confinement, individuals acquitted by reason of insanity could actually be committed for longer terms than if they were found guilty.

According to one key informant, David Guthman, a Los Angeles District Attorney specializing in insanity cases in that county, the prison sentences associated with many offenses were subsequently increased by the legislature; this, in turn, increased the maximum term of confinement for insanity acquittees. The increasing terms of confinement plus the hospital's tendency routinely to keep patients to their maximum terms (19) may have resulted in defense attorneys becoming increasingly reluctant to use the insanity defense with their clients (personal communication from John Monahan, Ph.D., Atascadero State Hospital, April 1990). Data from our study lend some support to this hypothesis. Although we found no significant difference in the actual length of stay of insanity acquittees before versus after reform, the correlation between the "sentence or maximum term of commitment" and the plea rate was $r=-0.69$ ($df=20$, $p<0.001$). For every 1-year increase in sentence, there was a decrease of 1.4 units (pleas per 1,000 indictments) in the plea rate.

In regard to insanity defense reform in general, it remains to be seen which reforms have the effects desired by their proponents. Our earlier data from Montana (20) indicate that although abolishing the insanity defense dramatically lowered the number of successful pleas, the number of individuals entering the plea remained unchanged. What changed was how those pleading insanity were processed. Instead of being acquitted by reason of insanity and committed for treatment, they were found incompetent to stand trial and committed to the same institution.

Other data from our study in Georgia, where a guilty but mentally ill statute was enacted in 1982, reveal a temporary increase in the number of insanity pleas and acquittals followed by a modest decline (unpublished paper by Callahan et al.). Of interest, however, was an observed shift in outcome for some of the most serious offenders (those who committed murder) from not guilty by reason of insanity to guilty but mentally ill, thereby creating a new group of inmates with mental health needs.

Findings associated with our study of an Ohio reform in which the court of jurisdiction was changed from probate (civil) to criminal in an effort to give the criminal court judges control over commitment and release decisions revealed relatively minor changes after reform (21). A smaller percentage of individuals were acquitted of murder and fewer acquittees were hospitalized after the reform, but the volume of insanity cases remained unchanged, as did the length of commitment.

Clearly, the alteration of the insanity test in California in 1982 had no noticeable impact. The expectation of its proponents that it would reduce the volume of insanity acquittals appeared to have been met on the surface; however, in fact, the reform really did little. A decline in acquittals had begun before the reform. This decline simply continued. It was not accentuated or slowed by changing the insanity test. These findings in California demonstrate the limited impact of changing the insanity defense test. Rather, it appears that more encompassing, system-wide changes in criminal justice or mental health, such as determinate sentencing in California, are more likely to have a substantial impact. Beyond documenting the negligible impact of this reform, our research demonstrates how essential plea data are to an adequate depiction of the range of possible changes associated with insanity defense reform. Unless the "big picture" is part of research in mental health law, the context of psychiatric practice may be badly misrepresented.

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# Solvent-Associated Olfactory Dysfunction: Not a Predictor of Deficits in Learning and Memory

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*Objective: The aim of the study was to evaluate associations between olfactory dysfunction and aberrations in learning and memory after chronic occupational exposure to mixed hydrocarbon solvents. Method: This was a cross-sectional, epidemiologic study of 187 paint manufacturing workers. The authors administered quantitative tests of olfactory function (the University of Pennsylvania Smell Identification Test) and neurobehavioral function (eight computer- and examiner-administered tests of learning and memory) to workers for whom detailed information was available on lifetime occupational exposure to solvents. Results: Olfactory function test scores were positively correlated with performance on seven of eight of the tests of learning and memory in bivariate analyses. After adjustment for important confounding variables (i.e., age, vocabulary score, and cumulative exposure to hydrocarbon solvents) with multiple linear regression, olfactory function scores predicted performance only on the Wechsler Memory Scale Delayed Logical Memory test. Conclusions: Overall, the data did not reveal that olfactory dysfunction was correlated with decrements in various memory functions.*

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Olfactory function can be affected in a number of neuropsychiatric disorders, and olfaction has been receiving increasing attention in the psychiatric literature (1). For example, research has revealed olfactory dysfunction associated with Alzheimer's disease, Parkinson's disease, Korsakoff's psychosis, schizophrenia, and major affective disorders (1). Data on patients with Alzheimer's disease indicate that neurofibrillary tangles and plaques accumulate in key olfactory regions early in the disease and in greater quantities than in other brain regions (2). Notably, in several of these neuropsychiatric disorders, decrements in learning and memory are also prominent.

Olfaction, learning, and memory are also affected by exposure to common environmental and occupational agents. Dose-related declines in olfactory function have recently been associated with cumulative lifetime exposure to solvents (3) in paint manufacturing workers. Neurobehavioral function after exposure to solvents has been the subject of extensive investigation (4–6), and declines in learning and memory have been associated with such exposure. Thus, olfactory dysfunction has been associated with 1) several neuropsychiatric disorders that are notable for their deficits in learning and memory and 2) toxic exposures that cause decrements in learning and memory. However, the relationship between the deficits in olfaction and learning and memory have not been extensively studied. This is of great interest because the pathways subserving these three functions have much overlap, especially in the limbic areas of the brain (1, 7, 8). The hippocampus, amygdala, and parts of the temporal cortex are particularly important to olfactory ability and learning and memory.

Studies of brain-damaged, postsurgical, and epileptic patients (9–11) demonstrate that lesions to the aforementioned areas cause decrements in olfactory ability, but these decrements have rarely been compared to changes in learning and memory in such patients. One study (9) reported that unilateral anterior temporal lobectomy affected olfactory ability, but these changes were not associated with changes in learning or memory. Thus, although olfactory dysfunction and aberrations in learning and memory may

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coexist, such deficits have rarely been compared in the same individuals. The full implications of observations linking olfaction and learning and memory remain unresolved.

Ryan et al. (12) have reported on the coexistence of olfactory and neurobehavioral disorders in workers exposed to solvents. Those authors hypothesized that because 1) limbic structures in the brain are apparently very sensitive to a number of toxic insults and 2) their data revealed an association between cacosmia (self-reported unpleasant sensation of odors) and disorders of learning and memory, solvent toxicity in the CNS might occur through an effect on rhinencephalic structures. The study was limited by a lack of quantitative measurements of olfaction and solvent exposure and possible biases in the selection of the 34 study subjects. We report the evaluation of olfactory dysfunction as a predictor of deficits in learning and memory in 185 solvent-exposed workers who evidenced dose-related declines in olfactory function (3, 4) and in whom olfactory function, learning and memory, and solvent exposure were all quantitatively measured.

## METHOD

### Study Group

The study group (N=187) consisted of male production, maintenance, and warehousing workers at two paint manufacturing facilities in the United States. Both plants manufacture a variety of paints and coatings, use a number of solvents in their operations, and operate 24 hours a day on three shifts. Participation in the study was voluntary. At plant 1, 91% of the workers participated (97 of 107) and at plant 2, 64% of the workers participated (90 of 140). There was not any selection bias by job title, but there were no other data available on the nonparticipants. These two plants were notable for stable working populations with little job turnover during the plants' existence (3, 4, 13). The mean±SD age of the study participants was 41.6±8.8 years. There were 131 Caucasians and 56 blacks. The mean±SD number of years of education was 12.3± 1.6.

### Data Collection

Data were collected by groups of trained researchers in April and May 1988. Olfaction was measured with the University of Pennsylvania Smell Identification Test, a 40-item, standardized, quantitative test of olfactory function. This test has been described elsewhere (14). Briefly, it consists of 40 microencapsulated odorant strips in four test booklets; the odorant label strip is scratched with a pencil, smelled by the test subject, and then the answer is chosen from among four possible responses. The test is sensitive to a broad range of olfactory disorders at many points along the olfactory pathways and is highly reliable (14). This tool has been used to document the effects of age, gender, smoking, and a number of chemical agents on olfactory function (3, 14–16).

**TABLE 1. Summary Statistics of Main Study Variables for 187 Workers Exposed to Solvents**

| Variable | Mean | SD |
|---|---|---|
| University of Pennsylvania Smell Identification Test score[a] | 34.2 | 5.9 |
| Solvent exposure (ppm-years) | 140.1 | 111.8 |
| Vocabulary score | 39.7 | 12.2 |
| Learning test scores | | |
| Rey Auditory Verbal Learning Test, trial 5 | 12.0 | 2.2 |
| Serial Digit Learning, computerized[b] | 16.6 | 6.2 |
| Serial Digit Learning | 15.8 | 7.0 |
| Symbol-Digit Learning | 14.8 | 4.6 |
| Memory test scores | | |
| Benton Visual Retention | 8.3 | 1.7 |
| Wechsler Memory Scale | | |
| Visual Reproduction | 8.4 | 3.0 |
| Logical Memory | 8.2 | 3.4 |
| Delayed Logical Memory | 6.6 | 3.4 |

[a] Smell score data were missing for two subjects.
[b] Data were missing for one subject.

All participants completed an extensive battery of both interviewer- and computer-administered neurobehavioral tests. Data were missing for two subjects on the smell test scores, so the analyses consist of 185 study subjects, except where noted. There were eight specific tests of learning and memory that were assessed for their association with olfactory ability: the Wechsler Memory Scale Logical Memory and Delayed Logical Memory and Visual Reproduction (17), Benton Visual Retention (computer administered) (18), Rey Auditory Verbal Learning Test, trial 5 (19), Serial Digit Learning (presented verbally) (20), a computer-administered test of Serial Digit Learning (adopted from the World Health Organization computerized battery, presented visually), and the Symbol-Digit Learning test (21). The WAIS-R vocabulary subtest score was used as a measure of premorbid verbal intelligence (22).

### Assessment of Solvent Exposure

A cumulative exposure model in which exposure duration and intensity were equally weighted was used to calculate lifetime exposure to hydrocarbon solvents. Average intensity of exposure (parts per million) was multiplied by duration of exposure (years) for each job the worker had ever held at the plants and then summed into the cumulative exposure variable (parts per million-years). This exposure consisted mainly of airborne toluene, xylene, and methyl ethyl ketone vapors. Thirteen to 15 years of industrial hygiene sampling data were grouped according to 19 homogeneous and stable exposure zones (12 at plant 1 and seven at plant 2) and used as the intensity of exposure for jobs classified into one of the 19 exposure zones (13). Intensity of exposure (as an 8-hour time-weighted aver-

**TABLE 2. Correlations Between Continuous Study Variables for 185 Workers Exposed to Solvents[a]**

| | Correlation (r) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Variable | Age | Smel | CSer | SerD | Bent | VisR | Vocb | LogM | DelM | RAVL |
| Age | | | | | | | | | | |
| University of Pennsylvania Smell Identification Test score (Smel) | −0.29 | | | | | | | | | |
| Serial Digit Learning, computerized (CSer) | −0.35 | −0.13 | | | | | | | | |
| Serial Digit Learning (SerD) | −0.27 | 0.08 | 0.50 | | | | | | | |
| Benton Visual Retention (Bent) | −0.34 | 0.33 | 0.46 | 0.33 | | | | | | |
| Visual Reproduction (VisR) | −0.31 | 0.32 | 0.43 | 0.31 | 0.45 | | | | | |
| Vocabulary score (Vocb) | −0.25 | 0.37 | 0.27 | 0.33 | 0.49 | 0.51 | | | | |
| Logical Memory (LogM) | −0.10 | 0.25 | 0.21 | 0.26 | 0.29 | 0.34 | 0.48 | | | |
| Delayed Logical Memory (DelM) | −0.14 | 0.30 | 0.24 | 0.28 | 0.32 | 0.31 | 0.47 | 0.81 | | |
| Rey Auditory Verbal Learning Test, trial 5 (RAVL) | −0.47 | 0.21 | 0.25 | 0.22 | 0.34 | 0.30 | 0.26 | 0.23 | 0.25 | |
| Symbol-Digit Learning | −0.33 | 0.21 | 0.41 | 0.38 | 0.40 | 0.45 | 0.40 | 0.25 | 0.27 | 0.38 |

[a] $p<0.001$ for $r>0.24$; $p<0.005$ for $0.20<r<0.24$; $p>0.05$ for $r<0.15$ (all for absolute values of r).

age) ranged from 0.4 ppm for warehouse workers in plant 2 to 31.2 ppm for small-order operators in plant 1. Mean±SD duration of employment was 15.5±8.0 years for plant 1 and 13.6±4.0 years for plant 2. The stability of the exposure zones over time was assumed and supported by the lack of significant changes in process or control at either plant and the lack of trends in the available exposure data (13). Jobs held before employment at the paint plants were considered for solvent exposure and were included in the cumulative solvent exposure variable when such exposure could be reasonably quantitated. Analyses were performed with and without the inclusion of prior exposure in the exposure variable; the results were not sensitive to this exposure.

### *Data Analysis*

All data analysis was performed with the BMDP Statistical Software program on a personal computer. Detailed descriptive statistics were calculated for all study variables, and Pearson correlation coefficients were calculated for the relationships between all continuous study variables. The relationships between smell scores and the tests of learning and memory were first examined by dividing the smell scores into quartiles (although there was an uneven distribution of subjects in some of the groups that could not be corrected because of the distribution of scores on the University of Pennsylvania Smell Identification Test). Tests for linear trend (F test for linear contrast [23]) were calculated for the mean learning and memory test scores across the quartiles. These quartile data are presented for easier visualization, but all analyses were also repeated by using the smell score as a continuous independent variable.

Multiple linear regression was used to assess the predictive value of olfactory test scores (independent variable) on the tests of learning and memory (dependent variables) while potential confounding by age, vocabulary score, and solvent exposure were controlled. Age and solvent exposure were the main a priori confounding variables. Vocabulary score was discovered in the course of data analysis to control for the known ethnic and racial differences in olfactory identification ability (3, 14–16), and therefore was included in the models as an additional important confounding variable. Other variables (e.g., race, cigarette smoking, educational level, plant, shift) were screened for potential confounding of the association between smell score and learning/memory test scores; no other important confounding variables were discovered. Interactions between smell scores and age, vocabulary score, and solvent exposure were evaluated; because no interactions were significant at $p<0.05$, these interaction terms were not included in the final models. The final regression models were extensively evaluated for colinearity and by examination of residual versus predicted plots.

## RESULTS

The means and standard deviations of the main study variables appear in table 1. Pearson correlation coefficients for all continuous study variables are presented in table 2. Table 2 reveals that vocabulary score was correlated with both the smell identification test score and the tests of learning and memory (and thus was likely to be an important confounding variable). In addition, correlations between more similar tests (e.g., Logical Memory and Delayed Logical Memory or computerized Serial Digit Learning and interviewer-administered Serial Digit Learning) were generally higher than correlations between less related tests (e.g., Rey Auditory Verbal Learning Test and Visual Reproduction). Smell identification test scores were positively correlated ($p<0.005$) with all tests except the two Serial Digit Learning tests.

Smell identification test scores were then divided into quartiles for easier visualization of the data, and means of the tests of learning and memory were cal-

**TABLE 3. Unadjusted Mean Scores on Learning and Memory Tests, by Quartile of Score on the University of Pennsylvania Smell Identification Test, for 185 Workers Exposed to Solvents**

| Test | Quartile 1 (score≤33) (N=51) Mean | SD | Quartile 2 (score=34–35) (N=29) Mean | SD | Quartile 3 (score=36–37) (N=48) Mean | SD | Quartile 4 (score≥38) (N=57) Mean | SD | p[a] |
|---|---|---|---|---|---|---|---|---|---|
| Serial Digit Learning, computerized | 15.7 | 6.3 | 14.9 | 7.3 | 16.7 | 6.7 | 18.1 | 5.0 | 0.02 |
| Serial Digit Learning | 15.4 | 7.0 | 14.8 | 6.6 | 15.1 | 7.4 | 17.1 | 6.9 | 0.21 |
| Benton Visual Retention | 7.5 | 2.0 | 8.0 | 1.9 | 8.5 | 1.5 | 9.2 | 0.9 | 0.0005 |
| Wechsler Memory Scale | | | | | | | | | |
| Visual Reproduction | 7.1 | 2.7 | 7.6 | 2.9 | 8.6 | 3.2 | 9.7 | 2.4 | 0.0005 |
| Logical Memory | 6.9 | 2.4 | 8.4 | 3.8 | 8.6 | 3.6 | 9.1 | 3.6 | 0.002 |
| Delayed Logical Memory | 5.2 | 2.7 | 7.0 | 3.4 | 6.8 | 3.5 | 7.5 | 3.6 | 0.002 |
| Vocabulary score | 32.3 | 12.3 | 35.6 | 12.6 | 40.3 | 10.8 | 47.2 | 9.1 | 0.0005 |
| Rey Auditory Verbal Learning Test, trial 5 | 11.4 | 2.3 | 11.7 | 2.0 | 12.1 | 2.1 | 12.6 | 2.0 | 0.002 |
| Symbol-Digit Learning | 13.7 | 5.0 | 14.1 | 4.4 | 14.6 | 5.0 | 16.3 | 3.8 | 0.004 |

[a]From F test for linear contrasts.

culated for subjects in each score quartile. Table 3 presents these results with tests for linear trend of the four means. Mean scores of all the tests of learning and memory increased across the four smell identification test score quartiles (i.e., the better the performance on the test, the better the learning and memory scores); only Serial Digit Learning was not significant at $p<0.05$.

The smell identification test score was next used as a predictor (independent) variable in eight multiple linear regressions with the tests of learning and memory as the dependent variables (table 4). These models all included age, vocabulary score, and cumulative solvent exposure as important confounding variables. The results did not suggest that smell scores were a predictor of neurobehavioral measurements of learning and memory when the effects of these confounding variables were controlled. Additional models (data not presented) without control for solvent exposure did not alter this conclusion (i.e., the most important confounding variables were age and vocabulary score). There were no other important confounding variables and no significant interactions of any variables with the smell identification test score. Because cigarette smoking is known to affect olfactory function (3, 16), smoking status was added to the models in table 4 as a dichotomous (ever versus never and current versus not current) and continuous (pack-years) variable. There was no confounding by smoking status of the associations observed in table 4.

## DISCUSSION

Olfactory function was significantly and positively correlated with performance on seven of eight of the tests of learning and memory before adjustment for important confounding variables (tables 2 and 3). After adjustment for age, vocabulary scores, and cumulative solvent exposure, olfactory function predicted performance only on the Delayed Logical Memory test ($p=0.03$). If consideration is given to the issue of multiple statistical comparisons, then a single p value of 0.03 from eight analyses may have been a chance finding. Thus, the data do not suggest that olfactory function is a predictor of various memory and learning functions.

Ryan et al. (12) have postulated that solvents may preferentially affect rhinencephalic structures in the brain; if this were the case, changes in olfactory function might be associated with aberrations in learning and memory. Ryan et al. did not quantitatively measure olfactory function but rather used a self-reported measure, cacosmia, that referred to the unpleasant sensation of odors. There are a number of potential explanations for the findings of the present study: 1) solvents do not act centrally to cause olfactory dysfunction, 2) different and distinct CNS pathways subserve learning, memory, and olfaction despite the close anatomic proximity of the CNS centers of these abilities in the brain, 3) olfactory dysfunction (this study) and cacosmia (Ryan et al.) both result from the effects of solvents on the CNS, but at separate and distinct sites, and 4) olfactory recognition ability is a long-term, primitive memory, while the tests employed in this study evaluated short-term and intermediate memory only.

We favor the first explanation, that solvents do not act centrally to cause olfactory dysfunction, for three primary reasons. First, animal data suggest that the primary olfactory neuron is uniquely sensitive to the toxic effects of a number of inhaled chemical agents (24, 25). Second, previous studies suggest that olfactory dysfunction from CNS lesions such as those from surgical excision is relatively uniform across smell identification test items (11), while solvent-exposed workers appear to exhibit deficits in a subset of the test items (3); this implies that solvents may not act centrally to cause olfactory dysfunction. Finally, the olfactory neuron is in a particularly vulnerable position, separated from inhaled chemicals by only 30 μ of mucous (8, 26). It would thus seem a likely candidate to be the critical target organ of airborne chemical expo-

**TABLE 4. Linear Regression Results for University of Pennsylvania Smell Identification Test Score as a Predictor of Scores on Learning and Memory Tests for 185 Workers Exposed to Solvents[a]**

| Variable | Beta | Beta SE | $p^b$ |
|---|---|---|---|
| Serial Digit Learning, computerized | | | |
| Age | −0.2152 | 0.0519 | <0.004 |
| Solvent exposure | −0.0052 | 0.0042 | 0.22 |
| Smell identification test score | −0.0621 | 0.0808 | 0.44 |
| Vocabulary score | 0.1015 | 0.0392 | 0.01 |
| Serial Digit Learning | | | |
| Age | −0.1505 | 0.0581 | 0.01 |
| Solvent exposure | −0.0081 | 0.0047 | 0.09 |
| Smell identification test score | −0.1196 | 0.0904 | 0.19 |
| Vocabulary score | 0.1538 | 0.0438 | <0.004 |
| Benton Visual Retention | | | |
| Age | −0.0332 | 0.0125 | 0.01 |
| Solvent exposure | −0.0022 | 0.0010 | 0.03 |
| Smell identification test score | 0.0364 | 0.0195 | 0.06 |
| Vocabulary score | 0.0468 | 0.0095 | <0.004 |
| Wechsler Memory Scale | | | |
| Visual Reproduction | | | |
| Age | −0.0559 | 0.0224 | 0.01 |
| Solvent exposure | 0.0018 | 0.0018 | 0.33 |
| Smell identification test score | 0.0665 | 0.0349 | 0.06 |
| Vocabulary score | 0.1046 | 0.0169 | <0.004 |
| Logical Memory | | | |
| Age | 0.0066 | 0.0270 | 0.81 |
| Solvent exposure | 0.0046 | 0.0022 | 0.04 |
| Smell identification test score | 0.0632 | 0.0421 | 0.14 |
| Vocabulary score | 0.1366 | 0.0204 | <0.004 |
| Delayed Logical Memory | | | |
| Age | −0.0019 | 0.0272 | 0.94 |
| Solvent exposure | 0.0018 | 0.0022 | 0.41 |
| Smell identification test score | 0.0917 | 0.0423 | 0.03 |
| Vocabulary score | 0.1182 | 0.0205 | <0.004 |
| Rey Auditory Verbal Learning Test, trial 5 | | | |
| Age | −0.1032 | 0.0173 | <0.004 |
| Solvent exposure | 0.0006 | 0.0014 | 0.68 |
| Smell identification test score | 0.0167 | 0.0269 | 0.53 |
| Vocabulary score | 0.0229 | 0.0130 | 0.08 |
| Symbol-Digit Learning | | | |
| Age | −0.1210 | 0.0373 | <0.004 |
| Solvent exposure | 0.0034 | 0.0030 | 0.27 |
| Smell identification test score | 0.0300 | 0.0581 | 0.61 |
| Vocabulary score | 0.1274 | 0.0282 | <0.004 |

[a] Linear regression controlled for age, vocabulary score, and exposure to solvents.

[b] From beta/beta SE, which is equivalent to a t test.

sure. If it is the critical target organ, it is possible that the threshold of cumulative exposure or dose for the olfactory effects of solvents is lower than that for learning and memory effects. Thus, a correlation between olfactory dysfunction and aberrations in learning and memory may be observed in populations with higher levels of exposure.

It should be noted that the present study population exhibited exposure-related declines in several neurobehavioral tests as well as in olfactory function, even after control of important confounding variables (3, 4). Furthermore, in the present population test scores were generally worse than and exposure duration was approximately twice as long as in the group studied by Ryan et al. (12). Thus, it is unlikely that the present findings could be attributed to lower exposures, fewer affected individuals, or an attenuated range of the outcome variables.

The present study has several strengths. First, this was a cross-sectional study of all exposed workers in two paint manufacturing plants, so selection biases germane to the clinical setting would not be an important problem. Although the participation at one of the plants was less than desired (64%), exposure status (current job title) was not an important determinant of participation, so it is our feeling that selection bias by exposure status does not account for the results. Cross-sectional studies are prone to other sources of bias if worker turnover is high. For example, if disease affects exposure status (olfactory dysfunction allowed the worker to tolerate a higher level of exposure, so the worker was moved into a new job with higher exposure) or if affected workers leave the workplace, then the results of cross-sectional studies may be biased. This was not the case for these two plants. Second, the industrial hygiene data available for these two plants were unique in their completeness and extent. We were thus able to determine quantitatively the exposure to solvents in the two plants to a degree not generally possible. This is important because there are no biological measures of past solvent exposure; currently available measures have relatively short half-lives and can only be used for acute exposures.

In conclusion, although olfaction and learning and memory functions are related anatomically and functionally, olfactory ability was not a predictor of performance on tests of learning and memory in 185 solvent-exposed workers who had evidenced exposure-related declines in these three functions. The results have implications regarding the possible mechanism of solvent-induced decrements in olfaction and learning and memory and the relationship among these three functions in the CNS. We hypothesize that solvents act peripherally to cause olfactory dysfunction and centrally to cause aberrations in learning and memory, and we await confirmation or refutation of these findings.

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# Long-Term Benzodiazepine Users 3 Years After Participation in a Discontinuation Program

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*Objective: Clinical status and use of benzodiazepines and other psychotropic drugs at follow-up were assessed in patients who had been chronically dependent on benzodiazepines and had been referred for participation in a discontinuation study. Method: Of 123 benzodiazepine-dependent patients screened for entry into a tapered discontinuation program, 48 had completed the program, 38 had not, and 37 had not undergone drug tapering. Follow-up information was obtained through a structured telephone interview and a mail questionnaire that included a global severity scale assessing anxiety and depression and the Hopkins Symptom Checklist. The time to follow-up was 2.7–5.0 years, and the mean±SD interval between screening and follow-up was 2.9±0.9 years. Results: Outcome at follow-up significantly favored the patients who had completed the discontinuation program; 73% were not using benzodiazepines, compared to 39% in the unsuccessful taper group and 14% in the no-taper group. Moderate or marked anxiety was still reported by 35% of the patients who were taking benzodiazepines and 25% of those who were not. At follow-up, 22% of the patients were being treated with nonbenzodiazepine psychotropic agents, primarily antidepressants. Conclusions: The high percentage of patients who were benzodiazepine-free at follow-up and the continued anxiety and depression present in many patients suggest that some patients may have been taking benzodiazepines because of chronic or recurrent anxiety or depression, not physical dependence.*

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The physician prescribing benzodiazepines for the treatment of the chronically anxious patient has to constantly weigh the benefits and risks of such use. On the one hand, there is accumulating evidence that both generalized anxiety disorder and panic disorder have significant chronicity (1–7); 50% or more of patients relapse by 1–5-year follow-up, even if acute treatment led to remission. This suggests that maintenance drug therapy should be considered a treatment option for some patients. On the other hand, although maintenance benzodiazepine therapy has demonstrated efficacy in both generalized anxiety disorder (8, 9) and panic disorder (unpublished 1988 paper of E. Schweizer et al.), it places the patient at significant risk for developing physical dependence and a withdrawal syndrome upon benzodiazepine discontinuation (10). The prevalence of physical dependence and withdrawal after long-term therapy exceeds 50% even for patients taking modest therapeutic doses of benzodiazepines. In fact, in chronically dependent patients, successful short-term benzodiazepine discontinuation, defined as the ability to achieve a benzodiazepine-free state and to remain benzodiazepine-free for 3–5 weeks, ranges from 40% to 60%, depending on whether benzodiazepine discontinuation is abrupt or gradual (11–14).

Little research, though, has focused on the long-term outcome of benzodiazepine-dependent patients. Of particular interest is whether the population of chronically dependent patients, estimated to be approximately 1.5% of all U.S. adults (15), can remain drug-free for a prolonged period. Furthermore, how do those who remain benzodiazepine-free differ from those who restart benzodiazepine intake? Last, is there any evidence suggesting that continued treatment with benzodiazepines might be clinically indicated and not solely a sign of physical dependence?

In this report we summarize the results of a 3-year follow-up of 123 patients who were chronically dependent on benzodiazepines.

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## METHOD

### *Subjects*

The subjects who form the basis of the current report were all patients who had been screened for entry into our benzodiazepine discontinuation program between December 1982 and February 1986 and who were available for follow-up evaluation. A total of 167 patients had undergone the initial screening, of whom 123 (74%) were available for follow-up evaluation. The reasons for our inability to reach patients for follow-up were as follows: 39 patients had moved and could not be located, and five patients were located but refused to be interviewed. There were no significant differences between the patients who were available and those who were lost to follow-up on any clinical, demographic, or benzodiazepine treatment variable. However, the percentage of patients who could not be located for follow-up was significantly higher among the patients who had not actually participated in the discontinuation program (38%) than among those who had (20%) ($\chi^2=6.6$, df=1, $p<0.05$).

The 123 patients available for follow-up consisted of 58 men (47%) and 65 women (53%). Their mean±SD age was 47±14 years. Seventy-five (61%) were married, and 103 (84%) had at least a high school education. Their diagnoses at the time of the original evaluation, made according to the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (16), had been as follows: generalized anxiety disorder, N=48 (39%); panic disorder, N=23 (19%); major depressive disorder, N=22 (18%); other affective illness, N=10 (8%); and no current diagnosis, N=20 (16%). For the majority of these patients, an anxiety disorder had previously been diagnosed and had remitted.

At the time of the initial evaluation, 67 patients (54%) had been taking benzodiazepines with short half-lives (alprazolam, N=18; lorazepam, N=41; oxazepam, N=6; triazolam, N=1; temazepam, N=1), and their mean±SD duration of daily use was 6.0±5.2 years. Fifty-six patients (46%) had been taking benzodiazepines with long half-lives (diazepam, N=37; clorazepate, N=13; chlordiazepoxide, N=3; flurazepam, N=1; halazepam, N=1; prazepam, N=1), and their mean±SD duration of daily use was 9.0±5.8 years. For benzodiazepines with short half-lives, the pretaper mean±SD daily dose, in diazepam equivalents (5 mg diazepam=7.5 mg clorazepate dipotassium=1.0 mg lorazepam=0.5 mg alprazolam), was 21.6±18.4 mg and the range was 2.5 to 90.0 mg. The pretaper daily dose for the long-half-life drugs was 15.5±15.3 mg, and the range was 2.5 to 95.0 mg. Overall, 84 patients (68%) had failed at least one previous attempt to stop taking benzodiazepines with or without a physician's help.

The patients were divided into two groups—the 86 patients who had participated in the original taper program (taper group) and the 37 patients who had not participated in the taper study and, after screening, had been referred back to their psychiatrists or family physicians in the community (no-taper group). Of these 37, eight had been excluded from the taper study for medical reasons, eight for administrative reasons (e.g., unable to keep appointments), and 21 because of patient decision. There were no significant differences between taper study participants and nonparticipants in sex, age, marital status, education, diagnosis, duration or dose of benzodiazepine therapy, or drug used. Upon completion of the benzodiazepine discontinuation program, the study participants had been referred back to their psychiatrists or family physicians in the community. All subsequent treatment was naturalistic.

**TABLE 1. Benzodiazepine Treatment Status at 3-Year Follow-Up Among 123 Patients Screened for Taper Program**[a]

| | | Benzodiazepine Status at 3-Year Follow-Up | | | |
|---|---|---|---|---|---|
| | | Not Using | | Using | |
| Taper Program Outcome | N | N | % | N | % |
| Not using benzodiazepines | 48 | 35 | 73 | 13 | 27 |
| Using benzodiazepines | 38 | 15 | 39 | 23 | 61 |
| Did not participate in taper | 37 | 5 | 14 | 32 | 86 |

[a] $\chi^2=30.4$, df=2, $p<0.001$.

### *Procedure*

Information for the current report was obtained through a structured telephone interview conducted by a research assistant (R.F.) with 20 years of experience. This telephone interview was supplemented by a mail questionnaire that inquired about current psychiatric treatment and drug use and included a 10-point global severity scale assessing current intensity of anxiety and depression and the Hopkins Symptom Checklist (17).

The time to follow-up ranged from 2.7 to 5.0 years, and the mean±SD interval between screening and follow-up was 2.9±0.9 years.

Categorical data were compared with chi-square analysis. For continuous variables we used a two-tailed t test or an analysis of covariance to control for differences in scores at screening. Significance levels were conservatively expressed as two-tailed.

## RESULTS

### *Benzodiazepine Use at Follow-Up*

Of the 123 patients who were available at follow-up, 55 (45%) were not taking any benzodiazepines. Table 1 shows the significantly favorable effect of study intervention on long-term benzodiazepine-free outcome. Seventy-three percent of the patients who successfully completed the taper program and 39% of those who did not, but only 14% of the patients who did not participate in the taper program, were benzodiazepine-free at follow-up.

Of the 68 patients who were taking benzodiazepines at follow-up, including no-taper patients, the patients who had originally successfully discontinued benzodiazepine use had the lowest mean±SD daily intake (8.3±5.7 mg/day, expressed in diazepam equivalents), the no-taper group had the highest intake (18.1±17.5 mg/day), and the originally unsuccessful taper group was intermediate (14.8±12.2 mg/day) ($F=2.17$, $df=2, 64$, $p<0.12$).

Of the 13 patients who had refrained from benzodiazepine intake for at least 5 weeks after discontinuation but later resumed benzodiazepine treatment, nine (69%) had restarted benzodiazepine therapy within 3 months of completing the taper program. The reasons patients gave for resuming benzodiazepine therapy were persistent insomnia (N=5), return of anxiety (N=3), symptoms of depression (N=2), panic anxiety (N=1), tension headaches (N=1), and colitis (N=1).

We attempted to identify which variables might have contributed to a benzodiazepine-free outcome at follow-up. We performed a search logistic regression analysis of all patients available at follow-up (N=123). Benzodiazepine treatment status at 3-year follow-up was the outcome measure used. Eight variables with zero-order correlations of $p<0.20$ were identified as potential predictors of benzodiazepine-free outcome. Interestingly, presence of prior withdrawal experience was unrelated to follow-up outcome ($\chi^2=0.3$, $df=1$, n.s.). Five of these variables (diagnosis, sex, daily dose of benzodiazepine, combined scores on the Hamilton Rating Scales for Anxiety and Depression, and benzodiazepine half-life) did not contribute significantly to the model. However, three variables were identified as significant predictors of benzodiazepine-free outcome: participation in the taper program ($p<0.001$), shorter length of benzodiazepine treatment ($p<0.01$), and younger age ($p<0.02$) (overall model: $\chi^2=36.02$, $df=3$, $p<0.001$).

### *Other Treatments Used at Follow-Up*

Of the 68 patients who were taking benzodiazepines at follow-up, 15 (22%) reported use of additional psychotropics: antidepressants, N=8; neuroleptics, N=5; and hypnotics, N=2. Of the 55 patients who were benzodiazepine-free at follow-up, 12 (22%) reported use of other psychotropics: 11 were taking antidepressants, and one was taking a hypnotic.

The reasons given for antidepressant use among the 19 subjects who were taking antidepressants were depression, N=10 (53%); insomnia, N=4 (21%); anxiety, N=3 (16%); panic attacks, N=1 (5%); and chronic pain, N=1 (5%). The doses of tricyclic antidepressants ranged from 20 mg/day (for insomnia) to 250 mg/day (for depression). Interestingly, 19 (22%) of the 86 taper patients but only two (5%) of the 37 no-taper patients were taking antidepressants at follow-up ($\chi^2=3.97$, $df=1$, $p<0.05$). Involvement in the taper program appeared to result in a reassessment of diagnosis and medication needs.

Overall, 76% of the patients who were taking antidepressants reported that psychiatrists had prescribed them, and only 24% reported such prescriptions by family physicians ($\chi^2=3.6$, $df=1$, $p<0.10$). In addition to drug therapy, 23 (27%) of the taper patients and 13 (35%) of the no-taper patients were in psychotherapy with psychiatrists or psychologists at follow-up. Of the 30 patients being treated for emotional symptoms by their family physicians, all but three were receiving benzodiazepines. In a comparison of patients who had participated in the taper and those who had not, irrespective of their outcome at follow-up, we found that significantly more of the no-taper than taper patients had consulted psychiatrists or family physicians (70% versus 47%; $\chi^2=5.0$, $df=1$, $p<0.05$).

### *Clinical Status at Follow-Up*

Anxiety and depression levels, assessed with the anxiety and depression factors of the Hopkins Symptom Checklist, were significantly lower for the patients who were not taking benzodiazepines at follow-up than for those who were. The mean±SD scores at follow-up, adjusted for pretaper baseline, were 1.65±0.5 and 1.89±0.5, respectively, for the anxiety factor ($F=5.67$, $df=2, 106$, $p<0.02$) and 1.61±0.5 and 1.91±0.5 for the depression factor ($F=8.22$, $df=2, 106$, $p<0.005$).

Anxiety and depression levels at follow-up did not differ significantly as a function of whether or not the patients had received additional antidepressive or other nonbenzodiazepine psychotropic medications.

Considering a mean item score of more than 2.00 on either the Hopkins anxiety or depression factor as indicative of clear-cut anxiety or depression, we observed that at follow-up 35% of the patients taking benzodiazepines (N=24) and 25% of the patients not taking benzodiazepines (N=14) still had substantial levels of anxiety. For depression, the respective percentages were 28% (N=19) and 25% (N=14).

On a 10-point global severity scale, on which 0 represented no symptoms and 10 represented greatest severity, the benzodiazepine-free patients had a mean±SD score at follow-up of 2.8±2.0 and the patients taking benzodiazepines had a score of 3.4±2.2; these scores are in the mildly symptomatic range and are not significantly different.

## DISCUSSION

The results of this study of 123 long-term benzodiazepine users showed that successful completion of a benzodiazepine discontinuation program resulted in benzodiazepine-free status at follow-up for a high percentage (73%) of patients. Even among patients who had been unsuccessful in the taper program, 39% were benzodiazepine-free at follow-up, whereas only 14% of the patients who had not participated in the taper program were benzodiazepine-free.

To put these results in context, it should be remembered that the daily benzodiazepine dose before tapering for the patient group under study was less than 40 mg of diazepam equivalents, although the benzodiazepine doses were in the therapeutic range. The average duration of use was 6 years for the patients taking short-half-life benzodiazepines and 9 years for the patients taking long-half-life benzodiazepines, and 68% of the study patients had failed previous attempts at benzodiazepine discontinuation. Therefore, if a selection bias is operating, it is most likely in the direction of making the patients under study a more taper-resistant group. As a result, generalization of our findings to nonstudy populations might be expected to yield an overly pessimistic prognosis for patients receiving long-term benzodiazepine treatment.

The only other comparable study of which we are aware was conducted by Golombok et al. (18). They reported results at 1.5-year follow-up for 46 long-term benzodiazepine users who had participated in a similar discontinuation program. They found 54% of their patients to be benzodiazepine-free at follow-up. In their study, the average duration of benzodiazepine use was approximately 10 years, and most patients also had failed previous attempts to discontinue benzodiazepine use, so those results also are likely to be biased toward a less favorable outcome than might be expected in general clinical practice.

The only predictors of benzodiazepine-free outcome that we were able to identify were participation in the taper program, shorter duration of benzodiazepine use, and younger age. Interestingly, neither shorter duration of benzodiazepine use nor younger age was found to correlate with withdrawal severity in our earlier studies (12, 13), so the influence of these two variables on outcome apparently is not mediated through their effects on withdrawal severity. It is possible that longer duration of benzodiazepine use is actually a marker for greater chronicity of illness and the resulting continued need for symptomatic treatment. It is also possible that older patients who are long-term users may have developed greater psychological dependence on their benzodiazepines.

Perhaps more notable was the *absence* of several variables as predictors of long-term outcome: half-life of benzodiazepine used, mode of withdrawal (abrupt versus gradual), and daily dose did not make a difference in long-term ability to remain benzodiazepine-free. This result, together with our previous finding that these variables did not significantly contribute to withdrawal severity during tapering (13), provides clinicians with no empirical evidence to support avoidance of short-half-life benzodiazepines in favor of long-half-life benzodiazepines for maintenance therapy. Furthermore, although gradual discontinuation of benzodiazepine treatment may in many cases increase short-term patient comfort, our current results do not suggest that this translates into a better long-term outcome than that achieved by patients who undergo abrupt discontinuation, at least when the benzodiazepine is prescribed in low to moderate therapeutic doses.

At 3-year follow-up 42% of the 86 patients who had participated in the drug tapering were receiving benzodiazepines. Thirteen of these had successfully discontinued benzodiazepine treatment but subsequently resumed use—mostly within 3 months of benzodiazepine discontinuation and mostly because of recurrent symptoms of anxiety, panic, or insomnia. On average, even the patients who had not been successful in the taper program had achieved some reduction in their daily doses of benzodiazepines. In fact, only four of the 123 patients had increased their daily doses of benzodiazepine by more than 10 mg of diazepam equivalents. This finding of a general lack of benzodiazepine dose escalation with naturalistic follow-up is consistent with our findings from prospective treatment studies (8, 9), in which no escalation of benzodiazepine dose was observed. Apparently, in therapeutic users of benzodiazepines, dose escalation over time is unusual.

What about the clinical status of the patients at 3-year follow-up? Discontinuing chronic benzodiazepine therapy did not result in significant worsening of anxious or depressive symptoms. On the contrary, the patients who were not taking benzodiazepines at follow-up had less anxiety and depression. It is possible, of course, that a partial or complete remission in clinical symptoms was the precondition which permitted these patients to remain benzodiazepine-free. Despite this overall improvement, 25% of the patients who were not taking benzodiazepines and 35% of the patients who were taking them continued to complain of at least moderate levels of anxiety. Furthermore, of the 50 taper participants who were not taking benzodiazepines at follow-up, 40% had received alternative treatment for anxiety or depression: antidepressant medication (N=4), counseling (N=9), or both (N=7).

All this suggests that many of the patients in our program may have received chronic benzodiazepine therapy not only because of physical dependence but also because of chronic or recurrent anxiety or depression. As indicated in our recent review (19), there is growing evidence that many anxiety disorders are chronic or recurrent and have psychiatric comorbidity. For many patients in the current study, participation in a taper program provided an opportunity for a diagnostic reassessment and institution of new treatments, even if they did not always result in benzodiazepine discontinuation.

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# Replicated Psychometric Correlates of Schizophrenia

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*Objective: The authors' goals are to use scales from the MMPI hypothesized in their previous research to be correlates of liability to schizophrenia to differentiate* DSM-III *schizophrenia from bipolar and unipolar affective illness and to cross-validate these correlates in an independently ascertained sample of patients with Research Diagnostic Criteria (RDC) schizophrenia or affective disorder. Method: The criterion sample consisted of 83 patients consecutively admitted to a state-operated community mental health center. Diagnoses of schizophrenia; bipolar disorder, manic; and major depression were assigned by using* DSM-III. *The replication sample consisted of 60 adults with RDC diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder, and unipolar disorder who were parents of children in two samples collected for a study of offspring at high risk for schizophrenia and other psychopathology. After the patients in the criterion sample were classified by logistic regression analysis, the results were used to classify patients in the replication sample. Results: The MMPI indicators had adequate sensitivity, specificity, and predictive power for classifying schizophrenia, and there was a moderately high rate of diagnostic agreement between the MMPI and* DSM-III. *Cross-validation in the replication sample was successful. Overall, the MMPI index was an adequate inclusion and exclusion criterion not only for* DSM-III-*defined but also for RDC-defined schizophrenia. Conclusions: A psychometric index composed of the paranoid schizophrenia, psychoticism, and manifest hostility scales from the MMPI would be a cost-effective measure to increase diagnostic efficiency in future schizophrenia research and clinical practice.*

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Explicit criteria and structured interviews are used routinely in psychiatry and have increased the reliability of the diagnosis of schizophrenia; however, current classification systems are only partially overlapping and identify different groups of patients as schizophrenic (1). It is therefore unclear which (if any) set of criteria for schizophrenia offers the most valid definition. Such uncertainty is especially problematic in genetic research because accurate determination of phenotypes for underlying genotypes is essential. Sherrington et al. (2) found that the odds in favor of linkage of DNA markers to schizophrenia vary as a function of which individuals are included as affected. Subsequent attempts to demonstrate such linkage have been unsuccessful (3); replication of findings would be facilitated by development of more valid diagnostic definitions.

Robins and Guze (4) discussed five approaches to establishing validity of a psychiatric diagnosis, one of which uses psychological tests to refine assessment. Such taxonomic instruments can be used along with explicit diagnostic criteria in an ongoing empirical process to increase the accuracy of the classification of psychiatric illnesses (5, 6). We followed this line of reasoning (7, 8) and used psychometric indicators from the MMPI to provide convergent validity for schizophrenia defined by Research Diagnostic Criteria (RDC) (9).

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**TABLE 1. Characteristics of 83 Patients With *DSM-III* Schizophrenia or Affective Disorders**

| | Age (years) | | Sex | | Race | | Marital Status | | Education (years) | | Shipley IQ | | Zigler-Phillips Score | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diagnosis | Mean | SD | M | F | White | Nonwhite | Single | Not Single | Mean | SD | Mean | SD | Mean | SD |
| Schizophrenia (N=57) | 33.30 | 11.71 | 37 | 20 | 42 | 15 | 47 | 10 | 12.86 | 2.47 | 101.11 | 12.03 | 0.64 | 0.33 |
| Bipolar disorder, manic (N=16) | 31.62 | 9.04 | 7 | 9 | 11 | 5 | 11 | 5 | 13.81 | 2.48 | 102.20 | 10.73 | 0.78 | 0.25 |
| Major depression (N=10) | 31.70 | 12.11 | 2 | 8 | 7 | 3 | 7 | 3 | 13.80 | 2.20 | 110.00 | 7.07 | 0.81 | 0.22 |

Further analyses of MMPI data in the New York High-Risk Project (10), a longitudinal study of children of schizophrenic parents, showed that 1) the rate of deviance on a psychometric index was significantly higher in the offspring of schizophrenic parents than in either the offspring of parents with affective disorder or the offspring of parents without psychiatric morbidity (11), 2) a latent class of offspring with index deviance could be demarcated (12), and 3) the index deviance was familial (13). These findings led us to hypothesize that index deviance reflects liability to schizophrenia.

Additional evidence for this interpretation would be provided by demonstration of the utility of the MMPI index for classifying clinical illness. Our goals in the present investigation are to 1) use our psychometric index to differentiate *DSM-III* schizophrenia from both bipolar and unipolar affective illness in a state hospital sample and 2) cross-validate our index in an independently ascertained sample of patient-parents with RDC-defined schizophrenia or affective disorder from the New York High-Risk Project.

## METHOD

### *Criterion Sample*

The criterion sample consisted of patients admitted consecutively in 1981–1982 to the Massachusetts Mental Health Center, a state-operated community mental health center that is a major teaching hospital for Harvard Medical School. Patients were ascertained for a larger study investigating the impact of reorganization of services (14). Diagnoses were assigned on the basis of an independent evaluation by a research psychiatrist who followed the clinical algorithms in *DSM-III*. MMPI data were obtained from the clinical psychology service at the mental health center for those patients for whom there was agreement between the research psychiatrist's diagnosis and a well-documented *DSM-III* chart diagnosis made by the senior attending psychiatrist on the service to which the patient was admitted. The MMPI was typically given after the second but before the sixth week of hospitalization. Of the 83 patients who completed a valid MMPI, 57 had schizophrenic disorder, 16 had bipolar disorder, manic, and 10 had major depression.

Patients were given the Shipley Institute of Living Scale, an abbreviated measure of intelligence (15). Information from clinical records was used to score the Zigler-Phillips Social Competence Scale (16), which uses age, marital status, intelligence, education, occupation, and employment history; each item is rated on a 3-point scale (0=lowest category; 2=highest category), and the overall score is the mean of the subcategories. The poor premorbid adjustment of the patients reflects the chronicity and severe psychopathology frequently observed in state hospital inpatient settings. The patients' characteristics are given in table 1; the only significant group difference was the sex distribution for patients with schizophrenia and major depression: a greater percentage of the latter were women ($p<0.02$, Fisher's two-tailed exact test).

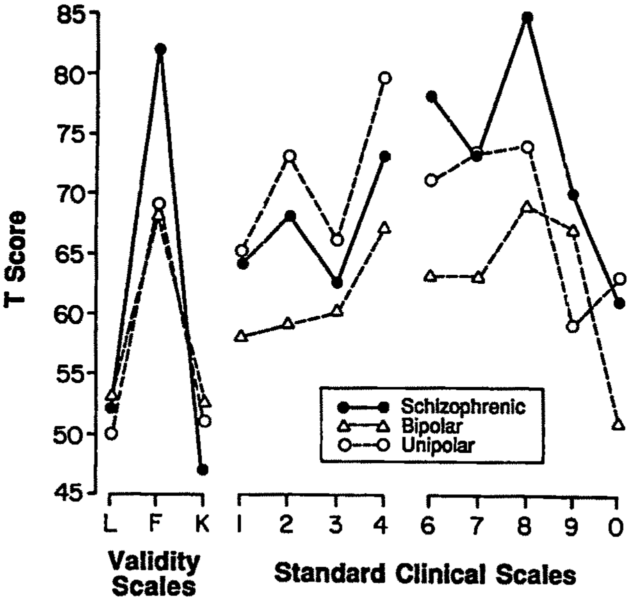
### *Replication Sample*

The replication sample consisted of psychiatrically ill adults who were parents of children in two samples collected for the New York High-Risk Project (10). Briefly, schizophrenic and nonschizophrenic patients were drawn from consecutive admissions to several state psychiatric facilities in the New York metropolitan area. Interviews with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (17) and hospital chart information were used to assign RDC diagnoses. Of the 61 patient-parents who completed a valid MMPI, 14 had schizophrenia, 17 had mainly schizophrenic schizoaffective disorder, five had mainly affective schizoaffective disorder, 13 had unipolar affective disorder, and 12 had bipolar affective disorder. A full description of the characteristics of these patients is given in our earlier reports (7, 8).

### *MMPI Variables*

The MMPI is a self-report instrument developed within a Kraepelinian framework. We reviewed the literature and found evidence that 13 MMPI indicators were potential correlates of liability to schizophrenia (11–13). These indicators measure an array of psychopathology (interpersonal aversiveness, disorganized thinking, anhedonia, decreased affective expression

**FIGURE 1. Mean T Scores on MMPI Validity and Standard Clinical Scales of 57 Patients With Schizophrenia, 16 With Bipolar Disorder, Manic, and 10 With Major Depression**[a]



[a] For the standard clinical scales, 1=hypochondriasis, 2=depression, 3=hysteria, 4=psychopathic deviate, 6=paranoia, 7=psychasthenia, 8=schizophrenia, 9=hypomania, and 0=social introversion.

and/or rapport, and avolition) and include scales L, F, K, and 4; a combination of scales 2, 7, 8, and 0; six Wiggins scales (social maladjustment, religious fundamentalism, psychoticism, phobias, manifest hostility, and hypomania); the 8-6 scale; and the paranoid schizophrenia scale. In our other reports (11–13), we combined these 13 indicators to form a psychometric index.

The MMPI administered by the clinical psychology service included 435 of 566 items. The omission of 131 items did not affect scoring of the standard scales; the 8-6, Wiggins, and paranoid schizophrenia raw scores were prorated. Standard scale and Wiggins raw scores were converted to T scores by using original normative sample means and standard deviations. For our criterion sample, paranoid schizophrenia scores were standardized by using mean±SD Veterans Administration norms (14.38±7.54); for the New York replication sample, we followed our previous practice (7, 8) of using paranoid schizophrenia plus mean±SD 1K norms (27.57±5.65).

A raw score on the L scale greater than 10 or an F score greater than 23 was used to declare four of our criterion sample profiles invalid. A set of criteria incorporating the TR and carelessness indexes (11) as well as an F-K score between −30 and −12 or between 23 and 64 was used to declare nine more of our criterion sample profiles invalid.

We submitted the nine standard and three validity MMPI scales to profile analysis (18), a multivariate procedure that contrasts the overall configural pattern (shape) of profiles in searching for qualitative distinctions in personality functioning that may reflect underlying disease states. Profile analysis was carried out with the SPSS-X multiple analysis of variance (MANOVA) program (19), which allows testing of the null hypothesis that the profiles are parallel; significant departure from parallelism implies different shapes.

We used the SAS LOGIST procedure (20) to fit logistic models. Group membership was the outcome Y; $Y=1$ corresponded to affected with schizophrenia and $Y=0$ corresponded to not affected with schizophrenia. Patients with bipolar disorder and those with major depression were combined in all analyses.

Logistic regression analysis of our criterion sample data was carried out by entering all 13 MMPI indicators from our index (11–13). We then used the "fast backward" stepwise option to eliminate nonsignificant variables ($p<0.05$). After classifying the patients in our criterion sample, we validated the $\beta$ weights and intercept obtained from the logistic regression analyses (technical details are available on request from Dr. Moldin) by using them to classify patients in the New York replication sample. The replication was performed by first including patients with schizoaffective disorder ($N=60$) and then excluding them ($N=38$).

Diagnostic efficiency was determined through specificity, sensitivity, positive predictive power, and negative predictive power calculations. We used the kappa coefficient as a measure of improvement over chance agreement between the MMPI and *DSM-III* or RDC diagnoses of schizophrenia. Receiver operating characteristic analysis (21) extended the evaluation of test (MMPI) performance and allowed comprehensive evaluation for all threshold decisions. The area under a receiver operating characteristic curve is a quantitative measure of the information content of the test; if a test lacks information content, the value for the area under the curve is 0.50. The LOGIST procedure calculated the area under the curve in our analysis of our criterion sample data; formulas described by Hanley and McNeil (22) were used to compute the area under the curve in the analysis of the New York High-Risk Project data.

## RESULTS

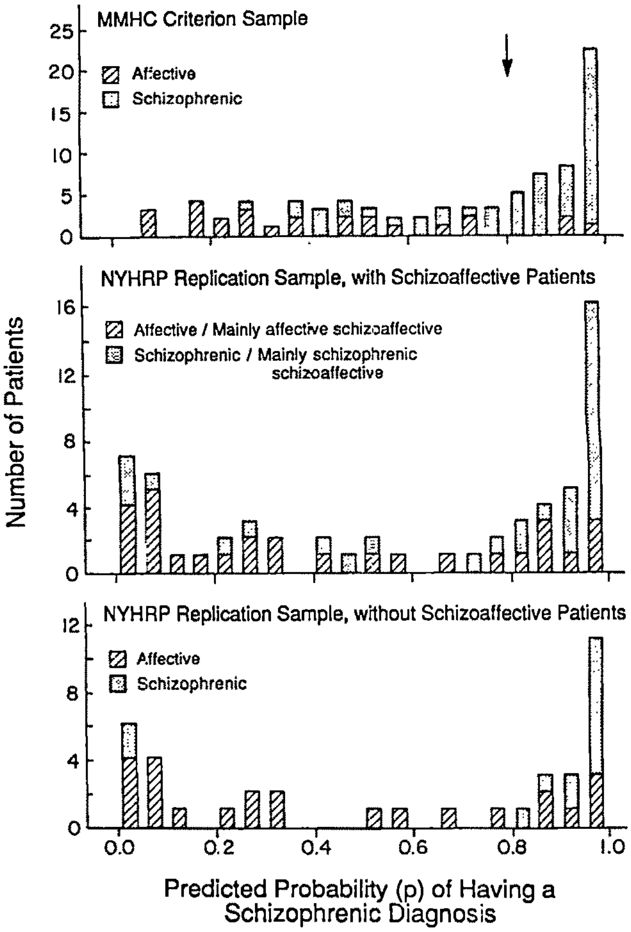
The group profiles of our criterion sample patients are presented in figure 1. The schizophrenic patients had the highest mean scores on scales 8 and 6; this code type is predictive of the illness as defined by several diagnostic criteria (23). The depressive profile is characterized by elevations on scales 4, 8, 2, 7, and 6, which are associated with unipolar depression (24). The relative elevations on scales 8, 9, and 4 that characterize the mean bipolar-manic profile in figure 1 are frequently associated with mania (24). Since profile elevations are state-dependent and vary according to the phase of affective illness (25), it is likely that the affective group profile represents a distortion resulting from the averaging of individual profiles. Such distortion is less likely to occur when schizophrenic profiles are averaged (7).

The parallelism hypothesis was rejected when the schizophrenic profile was compared with both the bipolar disorder (Hotelling's $T^2=25.17$, $F=2.01$, $df=11, 61$, $p<0.05$) and major depression (Hotelling's $T^2=29.32$, $F=2.26$, $df=11, 55$, $p<0.03$) profiles in figure 1. These findings are consistent with the hypothesis that there are stable, enduring personality dispositions measured by the MMPI that differentiate schizophrenia from both bipolar and unipolar affective illness.

A stepwise logistic analysis of the 13 MMPI scales and the sex variable resulted in a model with three variables (psychoticism, manifest hostility, and paranoid schizophrenia); sex was not retained in the model. The intercept was $-5.82$; the respective $\beta$ weights ($\pm$SE) for the three MMPI variables were $-0.13\pm0.06$ ($\chi^2=5.34$, $p<0.02$), $-0.10\pm0.04$ ($\chi^2=5.67$, $p<0.02$), and $0.35\pm0.09$ ($\chi^2=14.48$, $p<0.0001$). The relative odds of being affected given an MMPI score, as compared with the odds of being affected given an MMPI score one standard deviation lower ($e^{10\beta}$), were 0.27:1 for psychoticism, 0.35:1 for manifest hostility, and 33.60:1 for paranoid schizophrenia. The highest relative odds ratio was for the paranoid schizophrenia scale—the odds that a patient with a given paranoid schizophrenia score would have schizophrenia, compared with the odds that a patient with a paranoid schizophrenia score one standard deviation lower would have schizophrenia was nearly 34:1.

Figure 2 presents the distribution of p values (the probability of having a schizophrenic diagnosis) in our criterion sample and the New York replication sample with and without the patients with schizoaffective disorder. The first diagram shows the p distribution in our criterion sample; the second and third show those for the New York replication sample, when the $\beta$ weights and intercept from our criterion sample were used to classify cases. Cases with a predicted probability of 0.8 or more were classified as schizophrenic to minimize false positives. Given the results of our earlier psychometric analyses (7, 8) and other evidence (26, 27), we combined mainly schizophrenic schizoaffective disorder with schizophrenia and mainly affective schizoaffective disorder with affective disorders in the New York replication sample. The figures show that the criterion groups with schizophrenia and affective disorders were moderately separated; group discrimination was greater in the New York replication sample when patients with schizoaffective disorder were excluded.

**FIGURE 2. Probability of Schizophrenic Diagnosis According to Logistic Models Fitted to 83 Patients in the Massachusetts (MMHC) Criterion Sample and 60 Patients in the New York (NYHRP) Replication Sample[a]**



[a]There were 38 patients in the New York sample when patients with schizoaffective disorder were excluded. The arrow indicates the cutoff value for classification of schizophrenia ($p\geq0.8$).

Table 2 presents conditional probabilities, kappa statistics, and the values for the area under the curve for the logistic regression of MMPI data using our criterion sample $\beta$ weights and the intercept values. The indicators were relatively efficient in making correct classification decisions and performed adequately as inclusion (high positive predictive power) or exclusion (moderately high negative predictive power) criteria for a *DSM-III* diagnosis of schizophrenia. About 90% of the nonschizophrenic subjects in our criterion sample were classified on the basis of the MMPI as nonschizophrenic (high specificity). The indicators were successfully cross-validated in the New York replication sample; there was less sensitivity but greater negative predictive power. Diagnostic efficiency was greater when the patients with schizoaffective disorder were not included and when the classification cutoff was increased to $p\geq0.9$. RDC schizophrenia could be diagnosed or ruled out with confidence: more than 80% of the patients with affective disorders were classified as nonschizophrenic. The magnitude of kappa values in the two samples reflects moderate agreement between the indicators and schizophrenia as defined by both *DSM-III* and RDC. The value for the area under the curve for our criterion sample implies that, given pairs of randomly selected patients with affective and

**TABLE 2. Diagnostic Classification Results for the Criterion Sample of Patients With Schizophrenia or Affective Disorders and the New York Replication Sample of Patients With Schizophrenia, Schizoaffective Disorder, or Affective Disorder**

| Classification Result | Criterion Sample[a] (N=83) | Replication Sample: With Schizoaffective Disorder (N=60)[b] $p\geq0.8$ | $p\geq0.9$ | Replication Sample: Without Schizoaffective Disorder (N=38)[c] $p\geq0.8$ | $p\geq0.9$ |
|---|---|---|---|---|---|
| Sensitivity (true positives divided by true positives plus false negatives) | 0.68 | 0.64 | 0.55 | 0.86 | 0.71 |
| Specificity (true negatives divided by true negatives plus false positives) | 0.88 | 0.72 | 0.86 | 0.75 | 0.83 |
| Positive predictive power (true positives divided by true positives plus false positives) | 0.93 | 0.71 | 0.81 | 0.67 | 0.71 |
| Negative predictive power (true negatives divided by true negatives plus false negatives) | 0.56 | 0.66 | 0.64 | 0.90 | 0.83 |
| Kappa | 0.50 | 0.37 | 0.41 | 0.57 | 0.55 |
| Area under the curve | 0.87 | 0.74 | 0.74 | 0.80 | 0.80 |

[a]The base rate of schizophrenia was 0.69.
[b]The base rate of schizophrenia was 0.52.
[c]The base rate of schizophrenia was 0.37.

schizophrenic disorders, the probability (p, as determined from our logistic model) of the schizophrenic patient having the diagnosis of schizophrenia will be higher than that of the paired patient with affective disorder about 87% of the time. The figures for the area under the curve held up well on replication (0.74 and 0.80).

## DISCUSSION

Our analysis of MMPI index variables has demonstrated the efficiency of psychometric indicators for discriminating *DSM-III* schizophrenia from bipolar and unipolar affective illness. The index was validated in an independently ascertained sample of patients with RDC-defined schizophrenia and affective disorders. Although an expected diminution in overall classification efficiency in the replication sample was observed, the results show that the MMPI index was an adequate inclusion and exclusion criterion not only for *DSM-III*-defined schizophrenia but also for RDC-defined schizophrenia. Cross-validation was less successful when patients with schizoaffective disorder were included because of the greater psychometric overlap between mainly schizophrenic schizoaffective disorder and mainly affective schizoaffective disorder. This finding is consistent with there being less of a distinct boundary between syndromic variants of schizoaffective disorder than between "nuclear" forms of schizophrenia and affective illness (28).

Our best discriminating MMPI variable (the paranoid schizophrenia scale) was developed to identify schizophrenia-related psychopathology and was derived by comparing patients with schizophrenia diagnosed according to pre-*DSM-II* criteria with patients with other psychiatric disorders. Although diagnostic criteria have changed considerably over the years, we must emphasize that our findings do not reflect the completely independent validation of *DSM-III* and RDC diagnoses that would be provided by a laboratory measure derived from pathophysiological abnormalities. More than anything, the current investigation represents a useful heuristic approach for using MMPI indicators to converge with diagnostic criteria in more accurate classification of clinical schizophrenia in research and clinical contexts.

The very large β weight for the paranoid schizophrenia scale in our logistic model demonstrates its value in making differential diagnostic decisions between schizophrenia and bipolar and unipolar affective illness. The relative odds of having a schizophrenic diagnosis given a high paranoid schizophrenia scale score versus given a paranoid schizophrenia scale score one standard deviation lower were 34:1. A psychometric index composed of the paranoid schizophrenia, psychoticism, and manifest hostility scales would be a very cost-effective measure to increase diagnostic efficiency in future schizophrenia research and clinical practice. Scoring and administration of the relatively small number of binary items in the scales—112—can be done in a quantitative, objective, and standardized fashion.

Diagnostic error and imprecision have probably played a role in frustrating attempts to delineate etiologic and pathophysiological mechanisms in schizophrenia research. For example, current diagnostic criteria are not efficient in identifying individuals with unexpressed schizophrenic genotypes (29), who consequently would be false negatives. False positives are an even greater problem, especially in reducing the power of linkage analysis (30, 31). Kendler (32) found that evidence for linkage between a marker and a disease locus was highly dependent on the location of a diagnostic threshold. Without a "gold standard" for the schizophrenia genotype, all case definitions are best considered approximations of indeterminate validity of the true disease state (33). MMPI indicators are quantitative correlates that could be incorporated with other putative liability indicators (e.g., smooth pursuit eye movement dysfunctions, attentional-information processing deficits) into existing mathematical models (34), in which temporal stability is a criterion for greater reliability and accuracy of phenotypic assessments. Sensitivity, specificity, and true base rates for a lifetime diagnosis could then be estimated. These methods can be extended to allow for incorporation of the greater information content provided by quantitative indicators into genetic models, which in turn explicitly model diagnostic unreliability and error.

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# Bone Mineral Density and Anorexia Nervosa in Women

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*Objective: A review of reports of reduced bone mineral density in women with anorexia nervosa was undertaken in order to profile specific risk factors, which could then be used as the basis for suggestions for future research and treatment. Method: Thirteen research studies and four case studies of reduced bone mineral density and fractures in women with anorexia nervosa were reviewed. The relationships between bone mineral density and amenorrhea, estrogen, calcium intake, physical activity, parathyroid hormone, alkaline phosphatase, 1,25-dihydroxyvitamin D, cortisol, and growth hormone were examined in the reports of these studies and other reports of altered physiology during anorexia nervosa. Results: The average spinal, radial, and femoral bone mineral density in anorexic women was significantly lower than it was in normal control subjects. Concurrent with the low intake of nutrients by individuals with anorexia nervosa, low body weight, early onset and long duration of amenorrhea, low calcium intake, reduced physical activity, and hypercortisolism appeared more likely to contribute to decreased bone mineral density than did other abnormal aspects of the disorder. Conclusions: Future research needs to address how such factors as amenorrhea and hypercortisolism affect bone mineral density in anorexia nervosa. Since no controlled trials of estrogen replacement or calcium supplementation in anorexia nervosa have been reported, the proper treatment for decreased bone mineral density is not known. However, the most obviously important intervention is to encourage medical stabilization and weight gain.*

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There is currently considerable interest in the long-term adverse effects of anorexia nervosa on bone structure in patients with this disorder. Significant bone demineralization has been demonstrated with a variety of techniques both in case studies of fractures in women with anorexia nervosa and in research studies of women with the disorder. It is not precisely clear what physiological, endocrine, and behavioral factors associated with anorexia nervosa contribute to bone demineralization. The available studies, however, suggest a relatively consistent profile of the anorexic individual most at risk for significant bone demineralization.

In this article we first briefly address the processes involved in normal bone mineralization. Second, we describe methods of assessing bone density and review studies that have examined bone density in anorexic women. Then, because of the relationship between reduced bone mineral density and fractures, a discussion of case reports of anorexic patients with fractures is presented. Next, the relationship between amenorrhea and reduced bone mineral density is discussed. Finally, we discuss other physiological variables involved in the maintenance of bone tissue that might be altered in anorexia nervosa and note directions for treatment.

## BONE FORMATION AND RESORPTION

Bone formation and resorption (remodeling) is a continuous process. When bone resorption outpaces formation, demineralization occurs, which leads to osteoporosis. There are a number of chemical processes that appear to participate in the deposition and resorption of mineral into and out of bone, which in turn are part of an overall mechanism that controls serum calcium and phosphorus balance.

Calcium and phosphorus are regulated by controlling their absorption and excretion mainly through the actions of parathyroid hormone (PTH), 1,25-dihydroxyvitamin D, and calcitonin. PTH acts to maintain a balance between serum levels of calcium and phosphorus by increasing resorption of these minerals from bone. Secretion of PTH increases when calcium levels

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**TABLE 1. Results of Controlled Photon Absorptiometry Studies of Bone Density in Female Anorexic Patients**

| Study | Age Group | Diagnosis | N | Bone Mineral Density (percent of control value) | | |
|---|---|---|---|---|---|---|
| | | | | Radius | Spine | Femur |
| Biller et al. (7) | Adults | Anorexia nervosa | 19 | 97 | 58[a] | |
| | Adolescents | Anorexia nervosa | 7 | 103 | 91[a] | |
| Treasure et al. (8) | Adults | Anorexia nervosa | 31 | 93[a] | 82[a] | 77[a] |
| Newman & Halmi (10) | Adults | Anorexia nervosa | 18 | | 85[a] | 93 |
| | | Bulimia nervosa | 12 | | 95 | 101 |
| Mazess et al. (11) | Adults | Anorexia nervosa | 10 | | 79[a] | 87[a] |
| Davies et al. (12) | Adults | Anorexia nervosa | 26 | 88[a] | 86[a] | |
| | | Anorexia/bulimia nervosa | 26 | 90[a] | 90[a] | |
| | | Bulimia nervosa | 11 | 94 | 97 | |
| Bachrach et al. (13) | Adolescents | Anorexia nervosa | 18 | 94 | 79[a] | |
| Rigotti et al. (14) | Adults | Anorexia nervosa | 27 | 82[a] | | |
| Rigotti et al. (15) | Adults | Anorexia nervosa | 18 | 89[a] | | |
| Joyce et al. (16) | Adults | Anorexia nervosa | 8 | 95 | 89 | 85[a] |
| | | Bulimia nervosa | 17 | 97[a] | 98 | 94[a] |
| | | Eating disorder not otherwise specified | 8 | 87 | 87[a] | 77[a] |
| Anderson et al. (unpublished) | Adults | Anorexia nervosa (restricting) | 27 | | 90[a] | |
| | | Anorexia nervosa (bulimic subtype) | 35 | | 83[a] | |
| | | Bulimia nervosa (history of anorexia) | 15 | | 90[a] | |
| | | Bulimia nervosa | 13 | | 101 | |

[a] Significantly different from control value.

drop and decreases when calcium levels increase. This hormone facilitates retention of calcium and decreases retention of phosphorus through the kidney. PTH also increases the conversion of 1,25-dihydroxyvitamin D from its precursor, 25-hydroxyvitamin D, in the kidney (1).

1,25-Dihydroxyvitamin D, which is produced in the skin (as well as in the kidney) with exposure to ultraviolet light, directly stimulates the intestinal absorption of calcium and phosphorus. 1,25-Dihydroxyvitamin D also stimulates synthesis of collagen, alkaline phosphatase, and osteocalcin in the osteoblasts. Osteocalcin and alkaline phosphatase levels reflect the activity of the osteoblasts, which are the bone cells responsible for laying down the organic matrix and guiding the mineralization of bone (1, 2).

Calcitonin prevents bone resorption by decreasing calcium resorption from bone. Through this action and by increasing excretion from the kidney, serum levels of calcium are kept from rising too high.

Other hormones regulate and modify the effects of PTH, 1,25-dihydroxyvitamin D, and calcitonin. For example, although its actions on bone are not well understood, estrogen is thought to aid in the regulation of serum calcium by the enhancement of intestinal and renal absorption and may facilitate the maintenance of bone by inhibiting the secretion of bone resorption promoters (1).

## ANOREXIA NERVOSA AND BONE MINERAL DENSITY

Several methods for measuring bone mineral content have been used in experiments examining bone mineral loss in anorexic patients. Perhaps the most precise measure of bone density can be obtained by using photon absorptiometry. In single photon absorptiometry, developed by Cameron and Sorenson (3), bone mineral thickness is measured by scanning a collimated radioactive source over the bone. The beam intensity is measured with a scintillation detector after it passes through both soft tissue and bone. This method is best used for the appendicular skeleton (i.e., predominantly cortical bone in the arms and legs) (4). In dual photon absorptiometry, two separate photon energies are passed through bone and soft tissue in the axial skeleton (i.e., trabecular bone). The two separate energies are then measured, and the mass per unit area (grams per square centimeter) can be derived from both (4). Such a method is advantageous because of variation in bone marrow fat, which may be altered in anorexia nervosa (5, 6). However, it has been suggested that single photon absorptiometry is sufficient, especially for longitudinal studies, since a lower level of radiation is involved. Further, measures of bone mineral density taken with single photon absorptiometry correlate strongly with those taken with dual photon absorptiometry in the same individual (7).

Most reports of experiments using single and/or dual photon absorptiometry show that average bone mineral density is significantly lower in the lumbar spine and femoral neck in persons with anorexia nervosa than in normal persons (8–13). Lower bone mineral density in the radius has been found in some (8, 12, 14, 15) but not all (7, 13, 16) cases. Although bone remodeling occurs in both cortical and trabecular areas of bone, the more metabolically active bone is the trabecular portion; the lumbar spine contains 50% trabecular bone and the neck of the femur and the

**TABLE 2. Results of Controlled Radiographic Studies of Bone Density in Female Anorexic Patients**

| Study | Age Group | Diagnosis | N | Carpal Bone Measure |
|---|---|---|---|---|
| Crosby et al. (17) | Adults | Anorexia nervosa | 14 | Bone cortical area=79% of control value[a] |
| Ayers et al. (18) | Adolescents | Anorexia nervosa | 14 | Bone age=1–2 SD below normal in 11 patients |
| Lacey et al. (19) | Adolescents | Anorexia nervosa | 18 | Average radiological age=15.6 years; average chronological age=18.4 years |

[a] Significantly different from control value.

radius only 25% (15). Thus, it is possible that the difference in results in these reports occurred because the lumbar spine may best show the effect of anorexia nervosa on bone tissue. However, recent reports (11, 13) showed that the total skeletal mineral content in anorexic women (measured by whole-body dual photon absorptiometry) was 25% less than that in normal women.

Other studies measuring bone mineral density in patients with anorexia nervosa have used radiographs, the accepted technique prior to the availability of absorptiometry. Although this technique may not be as precise as photon absorptiometry, there have been consistent reports of decreased bone density in patients with anorexia nervosa. For example, Crosby et al. (17) found that the cortical area of the second metacarpus of the left hand was significantly lower in anorexic individuals than in normal subjects. Ayers et al. (18), using a microscopic measuring magnifier, found significant reduction of cortical thickness in the second metacarpus of the nondominant hand in anorexic subjects compared to that of control subjects. Lacey et al. (19) also found evidence of bone demineralization in 18 patients with anorexia nervosa who were under 18 years of age. Bone demineralization was determined by comparing radiographs of the radius, ulna, and carpal bones of patients with anorexia nervosa to the radiographs published by Greulick and Pyle in 1959. The radiological age of the bones of the anorexic patients was less than their chronological age, and the authors concluded that anorexia nervosa contributes to a cessation of bony development.

Table 1 shows the results from controlled studies measuring bone density with photon absorptiometry, and table 2 shows results with radiographic techniques. The experimental results we have reviewed indicate that, on average, a large number of anorexic patients have lower bone density in the lumbar spine, radius, wrist bones, and femur than that of normal persons.

Further, it appears that persons who have bulimia nervosa with concurrent or prior anorexic symptoms are more likely to have decreased bone density than those who have bulimia nervosa without such symptoms (10, 12, 16, and unpublished 1990 paper by A. Anderson and N. LaFrance).

While there is some evidence that decreased bone mineral density can be reversed following refeeding (9), it is not known how quickly density is restored, to what degree it is restored, and in what percentage of patients. One study (20) suggested that even after refeeding, bone density continues to decrease. Another study (14) indicated that there was no change in cortical bone density following recovery from anorexia nervosa.

## ANOREXIA NERVOSA AND BONE FRACTURES

Case studies of women with anorexia nervosa who experience bone fractures reveal consistently that such women have bone mineral density levels significantly below normal. Compression fractures of the lumbar spine have been reported (21–23). In some anorexic patients, multiple fractures and/or sites of reduced bone mineral density have been reported. Baum et al. (24) reported a 25-year-old white woman who had bilateral fractures of the ulna after beginning a weight-lifting program. This individual had also suffered a stress fracture of the right femoral neck 3 years earlier, and bone mineral density was significantly lower than normal in the lumbar spine and femoral neck. Three cases of young anorexic patients (mean age=24 years) reported by Brotman and Stern (21) revealed fractures in the pelvis, humerus, and sternum in addition to fractures in the lower spine and osteoporosis of the lumbar spine. Szmukler et al. (23) reported five older women with anorexia nervosa (mean age=45.5 years), four of whom had at least two vertebral fractures. Bone density of the distal ulna and spine showed osteoporosis. McAnarney et al. (25) reported a 25-year-old woman with anorexia nervosa who had a rib fracture possibly caused by forced vomiting. This individual also showed evidence of previous rib fractures. Recently, an anorexic subject with a hip fracture was noted to have bone densities that were 48% and 54% of normal in the spine and femur, respectively (11).

No estimates of the prevalence of fractures among anorexic persons with decreased bone mineral density are available. However, recent unpublished data from our clinic (J. Salisbury et al., 1990) show that 22% of 68 inpatients seen for treatment of eating disorders had spinal bone densities that were below the critical fracture threshold of 0.965 g/cm$^2$ (26). Newman and Halmi (10) reported that 10 of 18 anorexic patients had spinal bone densities at or below the fracture threshold. Additionally, in their unpublished 1990 paper, Anderson and LaFrance reported that 30% of the restricting anorexic subjects and 40% of the bulimic anorexic subjects in their study had bone densities below the fracture threshold. Rigotti et al. (14) estimated that the incidence of fracture among their anorexic patients was seven times higher than normal. These data indicate that a large percentage of patients may be at risk for developing fractures.

## PATHOPHYSIOLOGY OF BONE DEMINERALIZATION IN ANOREXIA NERVOSA

During anorexia nervosa, a number of physiological parameters are altered. We discuss first the relationship between estrogen, amenorrhea, and bone density in anorexia nervosa and then the role of calcium intake, because estrogen is involved with the maintenance of calcium balance. These characteristics are discussed in relation to postmenopausal women and female athletes, since a low serum estrogen level is characteristic of many women in both of these groups as well as women with anorexia nervosa. Finally, other physiological indices of bone function that may be involved in reduced bone mineral density in anorexia nervosa are discussed.

### *Amenorrhea and Estrogen*

Serum estrogen levels are low during amenorrhea. Amenorrhea often occurs concomitantly with the onset of anorexia nervosa, before significant emaciation occurs (7). Further, significant negative correlations have been reported between the duration of amenorrhea and bone mineral density in some (7, 8, 14, 18) but not all (12, 13, 15, 16) studies. Correlations between the duration of amenorrhea and bone mineral density range from −0.47 (8) to −0.53 (7). These correlations explain about 25% of the variance attributable to the differences in bone density. Thus, amenorrhea alone is not responsible for reductions in bone density.

Because the onset of amenorrhea often occurs concomitantly with anorexia nervosa, it is likely that the duration of anorexia nervosa will be similar to the duration of amenorrhea when patients are assessed. Accordingly, significant negative correlations between the duration of illness and bone density, ranging from −0.57 (15) to −0.63 (10), have been found.

Since there is little evidence for direct effects of estrogen on bone, such correlations probably reflect the effects of accruing food deprivation concurrent with a low serum estrogen level. Moreover, a significant correlation between degree of bone demineralization and serum estrogen level has not been demonstrated by most researchers. For the most part, studies have shown that serum estrogen levels are low in women with significant amounts of bone thinning (7, 9, 10, 13). Some case studies also demonstrate that estrogen levels are lower than normal among anorexic women who suffer spinal fractures but not among those who do not (21). However, some anorexic women with amenorrhea may have low levels of estrogen without exhibiting decreased bone mineral density, although this finding may be explained by the relatively shorter duration of the anorexia nervosa (18). These findings suggest that the important factor is not the absolute level of estrogen but the duration of time in which estrogen is low.

Since bone remodeling occurs at a greater rate in childhood and adolescence than in adulthood, the age at onset of amenorrhea may be important. Ayers et al. (18) showed that a greater degree of bone loss corresponded to onset of amenorrhea closer to menarche, and Biller et al. (7) noted that an onset of anorexia nervosa in adolescence, independent of duration, was related to decreased bone mineral density.

The mechanisms by which serum estrogen levels decrease in response to starvation are not well understood. Abnormalities of endocrine and hypothalamic function in patients with anorexia nervosa have been well documented (27), and decreased estrogen levels are usually attributed to food restriction rather than to a primary hypothalamic disorder (28). Food restriction may set the occasion for long-lasting hypothalamic dysfunction, since some neuroendocrine functions are not restored immediately after refeeding. Amenorrhea, for example, usually does not resolve immediately after refeeding (29). Other neuroendocrine functions are similarly affected. For example, vasopressin secretion is abnormal in anorexic patients and can persist after weight restoration (30).

### *Calcium Intake*

Estrogen regulates calcium mainly through the enhancement of intestinal and renal absorption. Because anorexic patients have low serum estrogen levels, their requirement for calcium may be increased. Anorexic patients are sometimes (17) but not always (7) deficient in their intake of calcium. For example, differences in average daily intake of calcium are not related to differences in radial bone density in patients with anorexia nervosa (13–15). However, the relationship between average daily intake of calcium and bone density in normal persons cannot always be established, although individuals with osteoporosis tend to have lower calcium intakes than normal individuals (31). Additionally, although average daily intakes might be normal, the lower estrogen levels of patients with anorexia nervosa may reduce the efficiency of calcium absorption. However, it is not known to what extent such patients are able to adapt physiologically. In the typical patient with anorexia nervosa, serum levels of calcium and phosphorus are, for the most part, normal (7–9, 17, 18). Thus, during starvation, serum calcium and phosphorus homeostasis takes precedence over the maintenance of bone tissue.

Unfortunately, there are no controlled studies comparing the bone mineral density of anorexic patients taking calcium and estrogen supplements to that of patients not taking such supplements. Preliminary data from our clinic suggest, however, that a long duration of calcium supplementation in patients with anorexia nervosa may have a beneficial effect on lumbar bone mineral density (unpublished 1990 paper by J. Salisbury et al.). In contrast, Rigotti et al. (14) reported that there did not appear to be a beneficial effect of calcium supplements on radial bone mineral density in anorexic patients.

There are many reviews and studies of the efficacy of estrogen and calcium supplementation in the maintenance of bone density in other populations. For example, Heaney and associates (31, 32) reviewed studies that reported calcium supplementation in postmenopausal women. These reviewers concluded that calcium supplementation is partially effective in offsetting or reducing the rate of bone loss. In contrast, estrogen replacement in postmenopausal women and women whose ovaries have been removed is very effective in the prevention of bone demineralization (33) and in reducing the risk of fracture (34). This treatment is most effective if started within 3 years of the loss of estrogen (35), and bone demineralization quickly resumes if estrogen is subsequently discontinued (36).

### *Physical Activity*

Another factor that contributes to the maintenance of bone density is physical activity. Since there are similarities between anorexia nervosa and some features of athletic training, it is instructive to examine the data regarding athletes with amenorrhea. Athletes with amenorrhea tend to have lower spinal bone density than athletes with normal menstrual cycles (37–40), are more likely to suffer from stress fractures (38, 40), and usually weigh less (39).

Although estrogen deficiency is apparent in amenorrheic athletes, these individuals have other characteristics that may play a role in decreased bone density. For example, age at the onset of training may be important. Marcus et al. (39) studied both amenorrheic and eumenorrheic runners and found that not only did the amenorrheic runners have lower estrogen levels and bone density but they also had begun training at or before menarche. The earlier onset of training may have contributed to these athletes' reduced bone mineral density by delaying or slowing the maturation of bone, similar to findings in anorexic women (7, 18). Additionally, although a correlation between estradiol concentrations and reduced bone mineral density in athletes has not been found (37), a significant negative correlation between duration of amenorrhea and bone mineral density has been noted (41). Furthermore, amenorrheic athletes have been reported to have a slightly (but not significantly) lower intake of calcium and calories than control subjects (39, 40). These findings suggest that, as in the anorexia nervosa patient, estrogen plays an indirect role in the reduction of bone density.

In contrast, there is evidence which suggests that some kinds of physical activity may prevent the loss of bone tissue. Athletes with amenorrhea have lower vertebral bone density than those with regular menses, but they have a higher density than amenorrheic sedentary women (39). In a report on women with anorexia nervosa (15), the more active individuals had higher radial density than those who were less active. In another study (16), moderate exercise had a protective effect but strenuous activity had a detrimental effect on bone mineral density in anorexic women. Another study (13) found no relation between levels of activity and bone mineral density in women with anorexia nervosa. Heaney et al. (31) suggested that exercise may improve absorption of calcium, since absorption efficiency decreases when patients are immobile. It has also been suggested that body weight itself enhances the mechanical stress of exercise on bone (42). Body weight (12) and body mass index (13) were positively correlated with bone mineral density in anorexic patients and normal control subjects. Thus, an extremely low body weight might attenuate the potential benefits of exercise for bone mineralization in women with anorexia nervosa.

### *PTH and Alkaline Phosphatase*

Physiological indices of bone function, such as serum levels of PTH (7, 14, 15, 43) and alkaline phosphatase (8, 9, 17, 18, 43), are normal in patients with anorexia nervosa. However, Matthews et al. (44) showed that serum alkaline phosphatase rose from low levels in parallel with weight gain in eight young patients (mean age=19 years) with anorexia nervosa, which they attributed to the resumption of bone growth.

### *1,25-Dihydroxyvitamin D*

It is not clear whether other physiological factors that play a role in the maintenance of bone density are altered in anorexic patients. For example, levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were shown to be normal by Rigotti et al. (14, 15). However, Fonseca et al. (43, 45) found significantly lower serum concentrations of 25-hydroxyvitamin D as well as lower bone density in anorexic subjects than in control subjects. Interestingly, levels of 1,25-dihydroxyvitamin D were normal (43). Fonseca et al. (45) attributed the low levels of 25-hydroxyvitamin D to the lower exposure to sunlight experienced by their patients in the United Kingdom.

In their more recent report (43), Fonseca et al. noted that anorexic patients with a reduced bone mineral index at the distal radius had significantly lower serum 25-hydroxyvitamin D, estradiol, and osteocalcin levels than did control subjects. There were no differences between the anorexic patients and the control subjects in serum levels of 1,25-dihydroxyvitamin D, PTH, phosphate, calcium, magnesium, or alkaline phosphatase. The authors attributed the osteopenia seen in these patients to the lower levels of osteocalcin (which is indicative of lower osteoblastic activity) rather than to vitamin D deficiency or hyperparathyroidism.

### *Cortisol*

Cortisol levels in anorexic patients are usually abnormally high. Since excess glucocorticoids tend to inhibit osteoblast proliferation and function (1), such hypercortisolism may contribute to the etiology of decreased bone mineral density in anorexic patients. The elevated serum and urinary cortisol concentrations appear to be due to increased production and decreased metabolic clearance (46, 47). Several reports have indicated that cortisol levels gradually decline during refeeding and return to normal after weight restoration (7, 48, 49). In addition, a significant negative correlation ($r=-0.43$) between cortisol excretion and bone density was recently demonstrated by Biller et al. (7). These findings suggest a role for hypercortisolism in the reduced bone mineral density seen in anorexia nervosa.

### *Growth Hormone*

There have been several reports of excessive levels of growth hormone in anorexic patients (50, 51). However, the actions of growth hormone are not direct but mediated by the somatomedins, which are low in anorexia nervosa. Interestingly, there is evidence that growth hormone may be able to increase the availability of 1,25-dihydroxyvitamin D (52).

## CONCLUSIONS

The available data suggest that the features which put an anorexic patient most at risk for developing significant bone demineralization are extremely low weight, prolonged amenorrhea, onset of anorexia nervosa in adolescence or before, hypercortisolism, and relative inactivity. In addition to low intake of other nutrients, calcium intake may be low. In such patients, serum estrogen and perhaps vitamin D and osteocalcin levels are low, but overall, other laboratory values of importance to bone homeostasis are normal. Finally, although most anorexic patients reported to have lower bone mineral density were young women, patients of all ages should be considered at risk if they have been amenorrheic for any length of time.

Future experiments need to address more precisely the roles of calcium intake, exercise, estrogen, and other hormones in the anorexic patient with low bone mineral density. These factors have been studied in other populations but have been largely ignored in anorexic patients with low bone mineral density. One possibility is a controlled, longitudinal study measuring the lumbar spinal density in anorexic patients before recovery and repeatedly after recovery. Such a study would address how quickly, to what extent, and in what percentage of patients bone density is recovered. The efficacy of estrogen and/or calcium supplementation in maintaining or restoring bone mineral density in these patients also needs to be established. Results of these experiments could suggest treatments for low bone mineral density in anorexic patients and describe more completely how bone homeostasis is altered during anorexia nervosa.

Pending the results of controlled intervention trials, we can only speculate about the proper prevention and treatment of low bone mineral density in anorexia nervosa. The most important intervention is obviously to address the illness directly and encourage medical stabilization and weight gain. However, given the fact that the treatment of anorexia nervosa is often prolonged and that many of these patients may be symptomatic for years, a strong case can be made for cyclical estrogen replacement therapy coupled with calcium supplementation.

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# Psychiatric Disorders in 36 Families With Wolfram Syndrome

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*Objective: The purpose of this study was to test the hypothesis that heterozygous carriers of the gene for the Wolfram syndrome, who constitute about 1% of the population, are predisposed to significant psychiatric illness. The Wolfram syndrome is an autosomal recessive neurodegenerative syndrome in which 25% of the individuals who are homozygous for the condition have severe psychiatric symptoms that lead to suicide attempts or psychiatric hospitalizations. Method: The authors collected questionnaires, death certificates, and hospital records for blood relatives and their spouses in 36 families of individuals with the Wolfram syndrome and compared the proportion of blood relatives who had had psychiatric hospitalizations, had committed suicide, or had self-reported mental illness to the proportion of spouses with the same manifestations. Results: The proportion of blood relatives who had had psychiatric hospitalizations, had committed suicide, or had self-reported mental illness significantly exceeded the proportion of spouses with the same manifestations. Conclusions: Since heterozygous carriers of the gene for the Wolfram syndrome are 50-fold more common among the blood relatives than among the spouses, the larger proportion among blood relatives is evidence that heterozygous carriers of the gene for the Wolfram syndrome are predisposed to significant psychiatric illness.*

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Identifying the specific genes that predispose individuals to psychiatric illness appears to be a formidable task. Linkage to polymorphic DNA markers in family studies has led to the successful cloning of genes for many distinctive Mendelian syndromes (1–3). However, no gene for any of the common psychiatric illnesses has been mapped unequivocally through linkage to DNA markers because 1) most families in which psychiatric disorders are prevalent do not show classic Mendelian inheritance patterns; 2) it is uncertain who in a family should be considered "affected," given that established diagnostic categories may not correspond to genetic entities in a one-to-one fashion; and 3) genes at different loci may predispose individuals to clinically indistinguishable illnesses (4).

An approach (5) that has been successfully used to identify genes that predispose individuals to cancer, diabetes mellitus, or cardiovascular disease may be particularly well suited to finding some of the genes that predispose individuals to psychiatric illness. There are autosomal recessive syndromes in which individuals who are distinctively homozygous for the syndromes have an extraordinarily high rate of a common chronic disease. Heterozygous carriers of the gene for any single autosomal recessive syndrome represent 0.5% to 1% of the general population when the prevalence of individuals who are homozygous for that syndrome is one in 40,000 to 160,000 (5). Thus, when heterozygous carriers of a specific gene have a high risk of a common disease, this gene must be considered important in predisposing members of the general population to the common disease. For example, individuals who are homozygous for ataxia-telangiectasia have a risk of cancer that is 60- to 180-fold greater than that of their age-matched peers (6). A high rate of breast cancer in 110 families with ataxia-telangiectasia showed that the ataxia-telangiectasia gene may account for 8%–18% of all breast cancers (7).

The Wolfram syndrome is an autosomal recessive neurodegenerative syndrome defined by diabetes mellitus and progressive optic atrophy, usually associated

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with diabetes insipidus, deafness, an atonic bladder, and diverse neurological abnormalities (8). In a genetic-epidemiologic study of this syndrome, we found reports of psychiatric symptoms in the clinical records of 41 of 68 patients who were homozygous for Wolfram syndrome (9) and frequent reports of such symptoms in their family members. To determine if the Wolfram syndrome gene also predisposed heterozygous carriers to psychiatric illness, we compared, in the families of these patients, the proportions of blood relatives and spouses who had had psychiatric hospitalizations, had committed suicide, and had self-reported mental illness.

## METHOD

From 1983 through 1986, we wrote to endocrinologists and ophthalmologists at major medical centers in the United States and to schools and institutes for the blind and asked them to refer any patients with Wolfram syndrome that they had seen. We identified 68 patients with Wolfram syndrome, from 36 white families, who met our criteria for diagnosis (9). Following procedures approved by our institution's committee on the protection of the rights of human subjects, patients and their families were contacted. To study the prevalence of disease in these 36 families, we asked that each parent, grandparent, sibling, aunt, uncle, and first cousin and his or her spouse and the closest living relative of deceased persons complete a questionnaire. Relatives were asked to list each time they had been a patient in a hospital, except for accidents or childbirth, and to respond to a checklist of conditions described in lay terms. Signed medical releases were obtained and used to retrieve hospital records for all major hospitalizations. For deceased persons, death certificates were retrieved. Since the original focus of the family study of Wolfram syndrome was to determine the prevalence of diabetes, no specific questions about hospitalizations for mental illness or symptoms of mental illness were asked, except for two checklist items that asked, "Have you ever had mental illness?" and "Have you ever had chronic nervous trouble?"

Questionnaires were completed for 522 blood relatives and 365 spouses. When the questionnaires, hospital records, and death certificates were received, the following items were entered into a computer file: 1) responses to each checklist item; 2) diagnoses from hospital records or doctors' notes, coded by a research assistant who used *ICD-8* codes; and 3) underlying and contributory causes of death from death certificates that were coded by a trained nosologist.

The 36 families contained 1,434 nonproband family members aged 20 years or older. We excluded 326 of them from the analyses we report here for the following reasons: lost to the family for follow-up (N=30); currently living, or died, in a country other than the United States (N=26); died before 1930 (N=12); living persons from whom we could not obtain a questionnaire (N=146); one proband refused to give us permission to contact the father's relatives (N=23); siblings of probands (N=52); and spouses of siblings of probands (N=37). The remaining 1,108 persons included 941 who were married or widowed (543 blood relatives and 398 spouses). All comparisons were based only on the married or widowed blood relatives and spouses, since a higher proportion of mental illness might be expected among single adult blood relatives. Further, the probands' siblings were excluded from comparisons because they might be unrecognized homozygous individuals; individuals who are homozygous for Wolfram syndrome have been shown to have a high rate of psychiatric illness (9).

The hypothesis that the Wolfram syndrome gene predisposes the individual to psychiatric illness was tested by comparing the blood relatives to the spouses for 1) the proportion with psychiatric hospitalizations or suicides, 2) the proportion who responded "yes" to the question about "mental illness," and 3) the proportion who responded "yes" to the question about "chronic nervous trouble." The odds ratios and Mantel-Haenszel chi-square statistics for age-stratified data, and corresponding p values, were calculated (10). The spouses were an appropriate comparison group because they were of comparable ages and shared ethnic origins and adult environments with the blood relatives.

The number of psychiatric hospitalizations and suicides are objective data that reflect severe behavioral disturbances that are unaffected by diagnostic inconsistencies. To determine which relatives had psychiatric hospitalizations, the complete records of each person for whom the items relating to mental illness or chronic nervous trouble were answered "yes," or for whom an *ICD-8* code between 290.0 and 309.9 (psychoses; other mental disorders) was recorded, were retrieved and reviewed blind as to blood relative or spouse status. The earliest age of documented psychiatric illness was determined from the available records.

**TABLE 1. Married or Widowed Blood Relatives and Spouses in 36 Families With Wolfram Syndrome**

| | Number of Blood Relatives | | | | |
|---|---|---|---|---|---|
| | | Probability of Heterozygosity[b] | | | |
| Age (years)[a] | Total (N=543) | 1.00 (N=78) | 0.50 (N=275) | 0.25 (N=190) | Spouses (N=398) |
| 20–29 | 55 | 1 | 8 | 46 | 52 |
| 30–39 | 93 | 5 | 11 | 77 | 96 |
| 40–49 | 113 | 19 | 44 | 50 | 91 |
| 50–59 | 90 | 27 | 48 | 15 | 53 |
| 60–69 | 85 | 19 | 64 | 2 | 51 |
| 70–79 | 73 | 4 | 69 | 0 | 38 |
| 80–89 | 29 | 2 | 27 | 0 | 15 |
| 90–99 | 5 | 1 | 4 | 0 | 2 |

[a] At death or end of study.

[b] The probabilities of heterozygosity, based on the relationship to the homozygous individual, were assigned as follows: parents, 1.00; grandparents, aunts, and uncles, 0.50; and first cousins, 0.25.

**TABLE 2. Psychiatric Illness in Married or Widowed Blood Relatives and Spouses in 36 Families With Wolfram Syndrome and 110 Families With Ataxia-Telangiectasia**

| | Wolfram Syndrome | | | | Ataxia-Telangiectasia | | | |
|---|---|---|---|---|---|---|---|---|
| | Blood Relatives (N=543) | | Spouses (N=398) | | Blood Relatives (N=1,595) | | Spouses (N=1,100) | |
| Measure of Psychiatric Illness | N | Age-Adjusted Proportion | N | Age-Adjusted Proportion | N | Age-Adjusted Proportion | N | Age-Adjusted Proportion |
| Psychiatric hospitalization or suicide | 12 | 0.019[a] | 2 | 0.004 | 10 | 0.006 | 7 | 0.007 |
| Self-reported "mental illness" | 12 | 0.019[b] | 2 | 0.005 | 15 | 0.010 | 8 | 0.011 |
| Self-reported "chronic nervous trouble" | 30 | 0.055[c] | 7 | 0.017 | 45 | 0.031 | 20 | 0.025 |

[a] Versus spouses in families with Wolfram syndrome, odds ratio=4.47 (Mantel-Haenszel chi-square [age-stratified] p=0.04); versus blood relatives in families with ataxia-telangiectasia, odds ratio=3.58 (p=0.002).

[b] Versus spouses in families with Wolfram syndrome, odds ratio=4.27 (p=0.05); versus blood relatives in families with ataxia-telangiectasia, odds ratio=2.22 (p=0.05).

[c] Versus spouses in families with Wolfram syndrome, odds ratio=3.12 (p=0.009); versus blood relatives in families with ataxia-telangiectasia, odds ratio=1.88 (p=0.02).

For statistical comparisons, patients were counted as having a psychiatric hospitalization only if their records were identified through these computer searches and we had received the medical records from the hospitalization or if another medical record made an explicit reference to the psychiatric hospitalization. Patients were considered to have committed suicide only if we received a death certificate that listed suicide as the cause of death.

To evaluate the possibility that the differences we observed between the blood relatives and spouses in the families with Wolfram syndrome were a consequence of the study design, we performed the same analyses of comparable data collected from 110 white families with ataxia-telangiectasia (7). We also compared the findings for the families with Wolfram syndrome and those with ataxia-telangiectasia. Ataxia-telangiectasia is an autosomal recessive syndrome in which individuals who are homozygous for the condition experience progressive cerebellar ataxia and other neurological manifestations and die in adolescence or early adult life from cancer or progressive pulmonary disease (6). In the 110 families with this condition, there were 1,595 blood relatives and 1,100 spouses who were aged 20 or older and were married or widowed. Completed questionnaires were received for 1,433 blood relatives and 925 spouses.

## RESULTS

The following analysis was based on 543 blood relatives and 398 spouses in the families with Wolfram syndrome, who were aged 20 or older and were married or widowed (table 1). As shown in table 2, a significantly larger proportion of blood relatives than spouses in the families with Wolfram syndrome had had a psychiatric hospitalization or had committed suicide or had self-reported mental illness or chronic nervous trouble. Four of the blood relatives had committed suicide, and two others had attempted to commit suicide. Among the psychiatrically ill blood relatives, nine had responded "yes" to the checklist item for mental illness.

In addition to these documented psychiatric illnesses in the statistical analyses, one blood relative in a family with Wolfram syndrome had a clear secondary mention of a psychiatric hospitalization that was not retrieved by searching through illness codes or checklist responses; three other blood relatives and one spouse reported psychiatric hospitalizations for which the relevant hospital records could not be retrieved. One sibling of a proband committed suicide.

Ataxia-telangiectasia is similar to Wolfram syndrome in that there is a high morbidity in adolescence and early adult life. In the families with this condition, however, the proportions of blood relatives with evidence of psychiatric illnesses were very similar to those of the spouses (table 2). Furthermore, psychiatric hospitalizations, suicides, and self-reported mental illness and chronic nervous trouble were significantly more common in blood relatives in families with Wolfram syndrome than in blood relatives in families with ataxia-telangiectasia. No differences between the spouses in the two groups of families were significant at the 0.05 level.

Seven of the psychiatrically ill blood relatives in the families with Wolfram syndrome had had multiple psychiatric hospitalizations. For nine of the 12 blood relatives who had had a psychiatric hospitalization or who had committed suicide, the earliest documentation of their psychiatric illness was before 45 years of age. Seven of the 12 were diagnosed as having depression or were described as depressed, and four were described as violent, angry, or hostile or had trouble with authority. Three of the hospitalized patients had evidence of psychotic thinking, and three had evidence of organic brain syndrome or had periods of confusion.

The parents of homozygous offspring and certain grandparents in consanguineous families are obligate

**TABLE 3. Psychiatric Illness in Obligate Heterozygote Relatives of Probands With Wolfram Syndrome**

| Subject | Relationship to Proband | Age (years)[a] | Psychiatric Findings |
|---|---|---|---|
| 1 | Father | 53 | Hospitalized for "depressive neurosis" after tranquilizer overdose; treated with amitriptyline, nortriptyline, and thioridazine; "not cooperative with his treatment" |
| 2 | Mother | 55 | Self-report of "chronic nervous trouble" |
| 3 | Mother | 52 | Hospitalized after drug overdose at age 17; medical records could not be retrieved |
| 4 | Mother | 32 | Hospitalized at age 27 for "nerves"; medical records could not be retrieved |
| 5 | Mother | 63 | Hospitalized at ages 33 and 63 for persistent dysphagia, weight loss, and anorexia without organic cause; treated with imipramine |
| 6 | Father | 60 | Hospitalized twice for "manic-depressive illness"; committed suicide with a gun |

[a] At death or end of study.

heterozygous individuals; they must carry the Wolfram syndrome gene. Of the 78 obligate heterozygous individuals in the study (ages 27 to 91; median=54 years), six stated that they had either mental illness or chronic nervous problems. Five of these reported psychiatric hospitalizations, although we could obtain medical records for only three (table 3).

## DISCUSSION

Each blood relative studied in the families with Wolfram syndrome had a prior probability of carrying the Wolfram syndrome gene of 0.25, 0.50, or 1.00, while approximately 1% (the prevalence of heterozygous individuals in the general population, estimated from our unpublished data) of the spouses were heterozygous for Wolfram syndrome. Thus, the highly significant difference between the blood relatives and spouses in the proportion of persons who had had psychiatric hospitalizations or had committed suicide or who had self-reported mental illness is the first evidence that individuals who are heterozygous for Wolfram syndrome are predisposed to psychiatric disorders.

From the data in table 2, it is possible to estimate the magnitude of the risk of psychiatric hospitalization or suicide associated with heterozygosity for Wolfram syndrome. The observed odds ratio comparing blood relatives and spouses was 4.47. Since approximately one-half of the 543 blood relatives were actually heterozygous for Wolfram syndrome (table 1), this is roughly equivalent to a greater than eightfold risk for carriers of the Wolfram syndrome gene compared to noncarriers. If this estimate is confirmed with more exact techniques (11) after the Wolfram syndrome gene is mapped or cloned, individuals heterozygous for Wolfram syndrome might account for almost 8% of all psychiatric hospitalizations or suicides in the United States if they represent 1% of the general population.

Psychiatric hospitalizations and suicides are objective events that can be counted reliably from hospital records and death certificates; the observed difference between the blood relatives and the spouses does not depend on arbitrary diagnostic categories. Although such records may underestimate the true prevalence of psychiatric disorders in these families, such underestimation is equally likely in both groups. Nondifferential underestimation may, in fact, lead to an underestimate of the difference between the two groups (10). Further, the comparison of blood relatives and spouses underestimates the difference between individuals who are heterozygous for Wolfram syndrome and those who do not carry the gene, since many of the blood relatives are not carriers of the Wolfram syndrome gene. The observed differences were not a consequence of our research design, since they were not found in the 110 families with ataxia-telangiectasia, who were studied in exactly the same way.

The prevalence of psychiatric hospitalizations and self-reported mental illness in this study should not be compared to prevalence estimates in epidemiologic studies that use different criteria for counting "cases" (12). Further, rates of psychiatric illness vary with age and differ widely among various ethnic groups and socioeconomic classes; while age matching or age adjustment is possible, it is not possible to identify a study population that is well matched for ethnicity or socioeconomic class to the set of families with Wolfram syndrome in the present study.

The most prominent psychiatric manifestations in individuals who are homozygous for Wolfram syndrome are depression, violent or assaultive behavior, and organic brain syndrome (9). Each of these was observed at a high frequency in the psychiatrically ill blood relatives in families with Wolfram syndrome, which suggests that these may be specific psychiatric symptoms associated also with heterozygosity for the Wolfram syndrome gene. The range of psychopathology associated with this gene can be determined precisely once heterozygous carriers can be identified with specific DNA probes.

Since the Wolfram syndrome is a classic Mendelian autosomal recessive syndrome, the gene for the syndrome can be mapped and cloned by using established molecular genetic techniques. When the Wolfram syndrome gene is tightly mapped to highly polymorphic markers, the association of this gene with psychiatric illness can be tested rigorously in families with Wolfram syndrome by using a new genetic method (11), and the range of psychopathology associated with the gene can be determined. Although there are no clinical or pathological clues to the metabolic action of the Wolfram syndrome gene, the mutated protein can be characterized through positional cloning. Understanding the metabolic action of the Wolfram syndrome gene will lead to specific effective measures to prevent or treat the psychiatric illness associated with this gene.

There are approximately 300 autosomal recessive syndromes that produce mental illness, dementia, or mental retardation in individuals who are homozygous for the syndromes (13); for each of these it is possible that there are clinically significant psychiatric effects in heterozygous carriers. The strategy outlined for the Wolfram syndrome gene can be applied to any of these syndromes. Identifying genes that predispose individuals to psychiatric disorders and understanding their metabolic basis will lead, in many instances, to effective preventive or treatment measures for these disorders.

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# Conditions Not Attributable to a Mental Disorder: An Epidemiological Study of Family Problems

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*Objective: The objective of this research was to identify and measure the differences among three groups of psychiatric outpatients: those with family problems but without mental disorders, those with both family problems and mental disorders, and those with a mental disorder but without family problems.* DSM-III *V code conditions (conditions not attributable to a mental disorder) other than family problems do occur, but family problems were chosen because of their importance. Method: All patients admitted to an outpatient psychiatric clinic during a 2-year period were studied (N=382). Of these, 92 had V code conditions unrelated to family problems and were excluded. Data are presented on the remaining 290 patients. Sociodemographic variables,* DSM-III *diagnoses, source of referral, previous and subsequent use of outpatient services, and type of family problem were examined. Patients were from a low-income population and came from three ethnic groups (white, black, and Hispanic). Results: Among whites, more men than women had family problems without mental disorders; among blacks, more women than men had family problems with and without mental disorders. Marital problems occurred most frequently in the group with family problems without mental disorders, and married subjects were more likely to have a V code condition. Professional referrals were more common than other referral sources in all three groups. However, family problems without mental disorders were more likely to occur among those who were referred by their families and had never had psychiatric treatment; patients with family problems and mental disorders were more likely to be self-referred and to have been previously treated; those with a mental disorder but without family problems were usually referred by professionals and almost always had been previously treated. There appeared to be underreporting of family problems among those with family problems and mental disorders and among black men with family problems with and without mental disorders. Conclusions: More research is needed on the patterns of use of outpatient psychiatric services by individuals with family problems and other V code conditions.*

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Although current estimates of the incidence and prevalence of mental disorders in the United States are now available, relatively less is known about the epidemiology of *DSM-III* V code conditions. These conditions are a focus of professional attention and treatment, but they are not attributable to a mental disorder. Examples include marital problems, parent-child problems, and other specified family circumstances. These family problems are important largely because of the reciprocal impacts of family dynamics and many, if not all, mental disorders (1–5).

The objective of this research was to identify and measure the differences among three groups of low-income psychiatric outpatients: those with family problems but without mental disorders, those with both family problems and mental disorders, and those with a mental disorder but without family problems. Low-income groups were chosen because both family problems and major mental disorders are quite common in these groups (6, 7).

## METHOD

The study setting was a university-affiliated, outpatient mental health clinic serving a low-income, inner-city population that resided within a catchment area.

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The study group consisted of all patients admitted to the clinic during a 2-year period. Patients with primary diagnoses of alcoholism or substance abuse were excluded; they were referred elsewhere. A comprehensive evaluation of each patient admitted was conducted by both a psychiatrist and a nonphysician psychotherapist. The Psychiatric Status Schedule (8) was completed, and diagnoses were based on *DSM-III* criteria. Family problems were defined as expressed conflicts between or among family members. A problem checklist was used to note whether a patient had a marital problem, a parent-child problem, or other specified family circumstances. Bivariate analyses were used to study the relationships between V code category and race-ethnicity and gender, marital status, *DSM-III* diagnosis, source of referral, and use of outpatient services.

## RESULTS

During the 2-year study period 382 patients were admitted to the clinic, with 85.0% coming from Hollingshead-Redlich class V (the lowest socioeconomic class) and 15.0% from class IV (6). Of these, 92 (24.0%) had no V code conditions related to family problems but had other V code conditions and were excluded. Table 1 shows the distribution of V code conditions in the remaining 290 patients.

Marital problems occurred most frequently among the 37 subjects with single V code conditions in the group with family problems but without mental disorders (45.9%, N=17). Other specified family circumstances occurred most frequently among the 120 subjects with single V code conditions in the group with both family problems and mental disorders (51.7%, N=62). Although marital problems and parent-child problems occurred in a small proportion of subjects (4.5%), about 25% of those in the group with family problems alone had both parent-child problems and other specified family circumstances, a combination that did not occur in the group with family problems and mental disorders.

Gender distribution differed by race-ethnicity. Among blacks, more women than men had family problems without (60.4%) and with (69.8%) mental disorders. Among whites, however, the same proportion of men and women (50.0%) had family problems and mental disorders; slightly more women (57.1%) had mental disorders but no family problems; and more men (61.1%) had family problems but no mental disorders. The percentage of patients with a V code condition was greater among those who had ever been married (86.0%) than among those who had never married (68.0%). In fact, about one-third (31.7%) of those who had never married had no identifiable V code condition.

In all three study groups, subjects were significantly more likely to be referred by professional agencies (i.e., mental health or other health agency or the court) than to be self-referred. These professional referrals, however, were less common in the groups with family problems and mental disorders (48.9%, N=67) and family problems alone (44.2%, N=34) than in the group with mental disorders but no family problems (55.3%, N=42). When these professional referrals were excluded from the analysis, subjects with family problems alone were most likely to be referred by their families (58.1%), those with family problems and mental disorders were usually self-referred (52.9%), and those with mental disorders but no family problems were likely to be self-referred (47.0%) or referred by their families (50.0%).

The majority of subjects with family problems alone (59.7%) had never before contacted the mental health treatment system. A smaller proportion of subjects with family problems and mental disorders had not previously used psychiatric services (37.2%). Subjects with mental disorders alone had usually been previously treated at a mental hospital (40.0%) or at a mental health center (31.0%).

In this study population, the median number of outpatient visits after the initial contact with the clinic was 10. This number was used to classify the patients into high users (more than 10 visits) and low users. The relationship between this variable and the type of V code category was statistically significant. After controlling for availability of mate or spouse and/or child, we examined differences among the three study groups in the mean number of outpatient visits following the initial contact with the clinic. The mean±SD numbers of outpatient visits were 8.3±9.2 for those with family problems alone, 25.6±30.9 for those with family problems and mental disorders, and 27.5±31.2 for those with mental disorders alone. Scheffé (9) post hoc pairwise comparisons of the three groups revealed that those with family problems and mental disorders and those with mental disorders alone were not significantly different in terms of the mean number of outpatient visits, whereas all other pairwise comparisons of group means were statistically significant ($p<0.05$).

## DISCUSSION

The differences among the three study groups in terms of gender and race-ethnicity may, at least in part, reflect underlying cultural differences. White men, for example, may be more willing to admit to family problems than are black and Hispanic men, thus producing among whites a more uniform distribution by gender of family problems and mental disorders. The male-female ratio for family problems and mental disorders was 0.47 for Hispanics, 0.43 for blacks, and 1.00 for whites. For family problems alone, the male-female ratio was 0.57 for Hispanics, 0.66 for blacks, and 1.57 for whites.

Both psychiatric and social services are badly needed

**TABLE 1.** ***DSM-III*** **V Code Conditions Related to Family Problems in Low-Income Psychiatric Outpatients (N=290)**

| | | Family Problems, No Mental Disorders (N=77) | | Family Problems and Mental Disorders (N=137) | | Mental Disorders, No Family Problems (N=76) | |
|---|---|---|---|---|---|---|---|
| Variable[a] | Total | N | % | N | % | N | % |
| V code condition | | | | | | | |
| Marital problem | 65 | 17 | 26.2 | 48 | 73.8 | 0 | 0.0 |
| Parent-child problem | 18 | 8 | 44.4 | 10 | 55.6 | 0 | 0.0 |
| Other specified family circumstances | 74 | 12 | 16.2 | 62 | 83.8 | 0 | 0.0 |
| Marital and parent-child problems | 13 | 4 | 30.8 | 9 | 69.2 | 0 | 0.0 |
| Marital problem and other specified family circumstances | 13 | 13 | 100.0 | 0 | 0.0 | 0 | 0.0 |
| Parent-child problem and other specified family circumstances | 19 | 19 | 100.0 | 0 | 0.0 | 0 | 0.0 |
| Marital and parent-child problems and other specified family circumstances | 12 | 4 | 33.3 | 8 | 66.7 | 0 | 0.0 |
| Race-ethnicity and gender[b] | | | | | | | |
| White | | | | | | | |
| Men | 32 | 11 | 34.4 | 12 | 37.5 | 9 | 28.1 |
| Women | 31 | 7 | 22.6 | 12 | 38.7 | 12 | 38.7 |
| Black | | | | | | | |
| Men | 50 | 19 | 38.0 | 19 | 38.0 | 12 | 24.0 |
| Women | 95 | 29 | 30.5 | 44 | 46.2 | 22 | 23.2 |
| Hispanic | | | | | | | |
| Men | 28 | 4 | 14.3 | 16 | 57.1 | 8 | 28.6 |
| Women | 54 | 7 | 13.0 | 34 | 63.0 | 13 | 24.0 |
| Marital status[c] | | | | | | | |
| Never married | 142 | 37 | 26.0 | 60 | 42.2 | 45 | 31.7 |
| Married | 64 | 29 | 45.3 | 26 | 40.6 | 9 | 14.0 |
| Separated, divorced, marriage annulled | 73 | 10 | 13.7 | 46 | 63.0 | 17 | 23.3 |
| Widowed | 11 | 1 | 9.1 | 5 | 45.4 | 5 | 45.4 |
| *DSM-III* diagnosis[d] | | | | | | | |
| Schizophrenia/schizoaffective disorder | 46 | 0 | 0.0 | 23 | 50.0 | 23 | 50.0 |
| Affective disorder | 36 | 0 | 0.0 | 24 | 66.7 | 12 | 33.3 |
| Adjustment disorder | 56 | 0 | 0.0 | 41 | 73.2 | 15 | 26.8 |
| Other axis I disorder | 51 | 0 | 0.0 | 31 | 60.8 | 20 | 39.2 |
| Axis II disorder | 24 | 0 | 0.0 | 18 | 75.0 | 6 | 25.0 |
| Source of referral[e] | | | | | | | |
| Self | 68 | 15 | 22.0 | 37 | 54.4 | 16 | 23.5 |
| Family | 67 | 25 | 37.3 | 25 | 37.3 | 17 | 25.4 |
| Mental health agency | 81 | 14 | 17.3 | 40 | 49.4 | 27 | 33.3 |
| Court | 16 | 11 | 68.7 | 4 | 25.0 | 1 | 6.2 |
| Other health agency | 46 | 9 | 19.6 | 23 | 50.0 | 14 | 30.4 |
| Other | 12 | 3 | 25.0 | 8 | 66.7 | 1 | 8.3 |
| Outpatient services | | | | | | | |
| Previous use[f] | 119 | 46 | 38.7 | 51 | 42.9 | 22 | 18.5 |
| More than 10 visits[g] | 137 | 19 | 13.9 | 75 | 54.7 | 43 | 31.4 |

[a] The mean±SD ages of the three groups were 31.6±14.6, 34.8±13.6, and 35.9±13.8 years, respectively (F=2.09, df=2, 1, p=0.13).

[b] $\chi^2=17.2$, df=10, $p=0.07$.

[c] $\chi^2=26.5$, df=6, $p<0.001$.

[d] $\chi^2=7.6$, df=4, $p=0.11$.

[e] $\chi^2=28.5$, df=10, $p=0.001$.

[f] $\chi^2=16.5$, df=2, $p<0.001$.

[g] $\chi^2=21.4$, df=2, $p<0.001$.

in low-income groups. This appears to have been obvious to health agencies and to the courts because 44% of the patients with family problems alone were referred by these professional groups.

The statistical association between marital status and the V code group was expected, given that two of the three V codes examined had to do with marital or parent-child problems. This association may also explain other findings, e.g., the fact that only 50% of patients with schizophrenia and schizoaffective disorder had family problems and the higher frequency of previous psychiatric treatment among patients with mental disorders but no family problems. Such patients are probably less likely to get married and have children and therefore less likely to have two of the three V code conditions.

Differences in diagnosis between the group with family problems and mental disorders and the group with mental disorders alone were not statistically significant. Although the numbers are small, this finding speaks against systematic bias associating the family problems noted with the diagnoses.

The fact that the group with family problems and mental disorders and the group with mental disorders alone did not differ significantly in terms of the mean number of outpatient visits suggests that family problems were underreported in the former group. In the group characterized by the coexistence of a mental disorder and a family problem, no attempt was made to determine whether the family problem exacerbated or was a byproduct of the mental disorder. Co-occurrence of disorders in clinic or hospital groups does not, of course, imply that the disorders coexist in the general population (Berksonian fallacy [10]).

This research should be repeated using ratings on axes IV and V of *DSM-III-R*, psychiatric diagnoses obtained by structured instrument, and clinicians' views on the etiology of the family problem. Future research should be aimed at monitoring the use of mental health services by individuals with family problems in a variety of treatment settings. Treatment outcome studies are needed to establish the legitimacy of the use of mental health services for such social problems.

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# Severity of Depression and Response to Cognitive Behavior Therapy

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*Objective: The authors studied the relationship between clinical severity of depression and response to cognitive behavior therapy. Method: Fifty-nine outpatients with major depression with endogenous features, according to Research Diagnostic Criteria, were stratified into more severe (score of 20 or more on the Hamilton Rating Scale for Depression; N=38) or less severe (Hamilton score of 19 or less; N=21) subgroups. Patients were treated with a 16-week, 20-session cognitive behavior therapy protocol. Outcome was assessed with the Hamilton scale, the Global Adjustment Scale, and the Beck Depression Inventory. Results: The more severe group was significantly more symptomatic across the 16-week protocol and had a significantly lower response rate on the Beck inventory (50% versus 81%). However, the groups did not significantly differ at end point on any of the three measures, and they showed comparable rates of symptomatic improvement (i.e., percent change in scores and interactions between severity classification and time). Conclusions: These results partially replicate the National Institute of Mental Health's Treatment of Depression Collaborative Research Program's findings of poorer response to cognitive behavior therapy in patients with Hamilton scale scores of 20 or more. However, both groups experienced robust and clinically significant reductions in depressive symptoms, and the response of the more severe patients in the current study could hardly be considered poor. While these findings do not support the view that a Hamilton scale score of 20 or more is a relative contraindication for cognitive behavior therapy, the symptoms of the more severely depressed patients did tend to remit less completely (particularly on the Beck inventory) and thus these patients may benefit from a more intensive or extended course of therapy.*

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Although cognitive behavior therapy is perhaps the best studied psychological treatment of unipolar major depression (1), significant questions persist about its efficacy in more severe depressive states (2, 3). Such concern may be reinforced by the recently reported findings of the Treatment of Depression Collaborative Research Program of the National Institute of Mental Health (4), in which cognitive behavior therapy (unlike interpersonal psychotherapy and imipramine) was found to be significantly less effective in more severe depression than in less severe depression. Further, cognitive behavior therapy was not found to differ significantly from a placebo-clinical management condition (4). These results, which represent the first published negative findings pertaining to cognitive behavior therapy, appear to be at variance with findings of earlier trials (5, 6) that examined the efficacy of cognitive behavior therapy in outpatients with moderate to severe depression. Moreover, the results did not seem consistent with our clinical experience. Nevertheless, because the Collaborative Research Program study was a well-controlled, randomized, multisite clinical trial conducted under the auspices of the National Institute of Mental Health, such findings are likely to have a significant impact on the field.

We therefore examined the relationship between severity of depression and clinical outcome in a consecutive series of depressed outpatients treated with cognitive behavior therapy. We used the definitions of severity and response employed by the Collaborative

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**TABLE 1. Clinical Characteristics of 59 Depressed Patients Treated With Cognitive Behavior Therapy**

| | Total (N=59) | | | | More Severe Depression[a] (N=38) | | | | Less Severe Depression[a] (N=21) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Item | N | % | Mean | SD | N | % | Mean | SD | N | % | Mean | SD | Statistical Analysis |
| Age (years) | | | | | | | | | | | | | |
| Current | | | 37.7 | 8.5 | | | 39.8 | 7.9 | | | 34.0 | 8.5 | $t=2.6^{b}$ |
| At onset | | | 31.0 | 10.9 | | | 32.3 | 11.1 | | | 28.7 | 10.5 | $t=1.2$ |
| Sex | | | | | | | | | | | | | $\chi^2=0.3$ |
| Male | 15 | 25 | | | 8 | 21 | | | 7 | 33 | | | |
| Female | 44 | 75 | | | 30 | 79 | | | 14 | 67 | | | |
| Marital status | | | | | | | | | | | | | $\chi^2=5.8$ |
| Single, never married | 17 | 29 | | | 10 | 26 | | | 7 | 33 | | | |
| Married | 29 | 49 | | | 16 | 42 | | | 13 | 62 | | | |
| Separated/divorced | 10 | 17 | | | 9 | 24 | | | 1 | 5 | | | |
| Widowed | 3 | 5 | | | 3 | 8 | | | 0 | 0 | | | |
| Employment status | | | | | | | | | | | | | $\chi^2=10.1^{c}$ |
| Employed outside home | 44 | 75 | | | 29 | 76 | | | 15 | 71 | | | |
| Homemaker | 5 | 8 | | | 5 | 13 | | | 0 | 0 | | | |
| Student | 4 | 7 | | | 0 | 0 | | | 4 | 19 | | | |
| Other | 6 | 10 | | | 4 | 11 | | | 2 | 10 | | | |
| Education (years) | | | 14.3 | 2.4 | | | 14.5 | 2.6 | | | 13.9 | 2.1 | $t=0.9$ |
| High school | 14 | 24 | | | 8 | 21 | | | 6 | 29 | | | |
| Some college | 22 | 37 | | | 14 | 37 | | | 8 | 38 | | | |
| College graduate | 11 | 19 | | | 6 | 16 | | | 5 | 24 | | | $\chi^2=2.7$ |
| Postgraduate work | 12 | 20 | | | 10 | 26 | | | 2 | 10 | | | |
| Previous episodes of depression | | | 1.5 | 1.4 | | | 1.4 | 1.5 | | | 1.6 | 2.5 | $t=0.3$ |
| RDC subtype | | | | | | | | | | | | | |
| Endogenous | | | | | | | | | | | | | $\chi^2=3.0$ |
| Probable | 9 | 15 | | | 3 | 8 | | | 6 | 29 | | | |
| Definite | 50 | 85 | | | 35 | 92 | | | 15 | 71 | | | |
| Occurrence | | | | | | | | | | | | | $\chi^2=1.9$ |
| Single episode | 28 | 47 | | | 15 | 39 | | | 13 | 62 | | | |
| Recurrent | 31 | 53 | | | 23 | 61 | | | 8 | 38 | | | |
| Pretreatment scores | | | | | | | | | | | | | |
| Hamilton depression scale | | | 21.1 | 3.4 | | | 23.3 | 3.0 | | | 17.1 | 1.8 | $t=9.9^{d}$ |
| GAS | | | 52.4 | 8.0 | | | 50.6 | 7.9 | | | 55.5 | 7.2 | $t=2.4^{c}$ |
| Beck Depression Inventory | | | 26.5 | 7.5 | | | 28.9 | 6.6 | | | 22.4 | 7.0 | $t=3.6^{b}$ |

[a] More severe=Hamilton depression score of 20 or more; less severe=score of 19 or less.
[b] $p<0.01$.
[c] $p<0.05$.
[d] $p<0.001$.

Research Program, as well as several alternative methods for classifying treatment outcome.

## METHOD

The patients included in this report were 59 subjects consecutively admitted to the Psychobiology of Recovery in Depression protocol, an ongoing longitudinal investigation of the recovery process in unmedicated depressed outpatients. This protocol is being conducted in the Cognitive Therapy Clinic of the Mood Disorders Module of the Western Psychiatric Institute and Clinic. The Mood Disorders Module was also one of the three clinical sites of the Collaborative Research Program study. However, our study protocol began about 1 year after the collaborative study ended, and there is no overlap in personnel or patients. Nevertheless, our protocol recruits from the same patient population as the earlier collaborative study and was the principal referral site for research-eligible depressed patients during the 24-month period in which this study group was collected.

Patients were selected for inclusion in the study on the basis of the following syndromal and symptomatic criteria: *DSM-III-R* diagnosis of major depression, diagnosis of probable or definite endogenous subtype of primary major depression (nonbipolar, nonpsychotic) according to the Schedule for Affective Disorders and Schizophrenia and Research Diagnostic Criteria (RDC), and Hamilton Rating Scale for Depression (7) score of 15 or more. Chronically depressed patients were excluded from the study; all patients' index episodes were 18 months or less in duration. These criteria were developed to yield a group of moderately to severely depressed outpatients with a relatively high probability of psychobio-

**TABLE 2. Test Scores at End of Treatment for 59 Depressed Patients Treated With Cognitive Behavior Therapy**

| | More Severe Depression[a] (N=38) | | | | Less Severe Depression[a] (N=21) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Item | N | % | Mean | SD | N | % | Mean | SD | Statistical Analysis |
| Categorical response | | | | | | | | | |
| Hamilton depression score≤6 | 24 | 63 | | | 18 | 86 | | | $\chi^2=2.3$ |
| Beck depression score≤9 | 19 | 50 | | | 17 | 81 | | | $\chi^2=4.2$[b] |
| End-point score | | | | | | | | | |
| Hamilton depression scale | | | 6.0 | 5.7 | | | 3.9 | 5.1 | t=1.5 |
| GAS | | | 81.7 | 14.7 | | | 87.5 | 12.2 | t=1.5 |
| Beck Depression Inventory | | | 9.2 | 8.6 | | | 5.2 | 6.8 | t=1.8 |
| Percent change in score | | | | | | | | | |
| Hamilton depression scale | | | 73.6 | 26.2 | | | 77.9 | 27.1 | t=0.6 |
| GAS | | | 64.5 | 36.5 | | | 60.0 | 31.4 | t=0.5 |
| Beck Depression Inventory | | | 66.6 | 30.9 | | | 76.4 | 28.9 | t=1.2 |

[a] More severe=Hamilton depression score of 20 or more; less severe=score of 19 or less.

[b] $p<0.05$.

logical disturbance. Patients were *not* selected on the basis of suitability for cognitive behavior therapy.

The criteria were applied to 110 unipolar depressed outpatients who were consecutively admitted during a 24-month period; 66 outpatients were considered eligible for participation following clinical evaluation. The principal reasons for excluding patients were chronicity of the index episode or insufficient number of endogenous symptoms for the RDC diagnosis. Two eligible patients declined to participate in favor of pharmacological treatment, and two other potentially eligible patients were referred for immediate treatment because of their degree of incapacity or suicidality. Sixty-two patients provided written informed consent for research participation.

After initial diagnosis and medical screening, persistence of depression was evaluated over a 14-day drug and alcohol washout period. Sixty patients still met entry criteria following the washout. They next began a 16-week, 20-session course of cognitive behavior therapy conducted by experienced therapists who received ongoing supervision. Clinical response was evaluated by independent raters according to the Hamilton depression scale and the Global Assessment Scale (GAS) (8) and by the patient-rated Beck Depression Inventory (9). Neither the raters nor the therapists were informed of the main hypotheses of the study, including plans to test clinical response as a function of severity. One patient withdrew from the protocol after one session of therapy. The remaining 59 patients completed a minimum course of 10 sessions of treatment with cognitive behavior therapy; 50 (85%) completed the entire protocol. The nine patients who terminated the protocol prematurely did not differ from the 50 who completed the protocol on any of the baseline measures.

In keeping with the methods of Elkin et al. (4), the study group was stratified into more severe (Hamilton scale score of 20 or more; N=38) and less severe (Hamilton scale score of 19 or less; N=21) groups. As summarized in table 1, the more severe group was significantly older and manifested significantly greater pretreatment symptoms on both the GAS and the Beck inventory. In addition, there were trends ($p<0.10$) suggesting that the more severe group was more likely to be separated or divorced and was more likely to meet the RDC for definite endogenous subtype.

The relationship between severity of depression and response to cognitive behavior therapy was evaluated by a series of six analyses. First, simple correlations were performed for the relationship between pre- and posttreatment scores on the Hamilton scale, GAS, and Beck inventory. Second, response at termination was defined by the two outcome criteria used in the collaborative study: Hamilton scale score of 6 or less and Beck inventory score of 9 or less. Response rates were calculated for all 59 patients (by using end-point scores for the nine patients who terminated the study prematurely); chi-square statistics (one-tailed, corrected for discontinuity) were used to test the significance of differences in response rates between the more and less severe groups. Third, pretreatment Hamilton scale, GAS, and Beck inventory scores were compared in patients categorized as responders or nonresponders by these definitions, through a series of two-tailed t tests. Outcome also was assessed by comparing week 16 (or end-point) scores and percent change in scores on depression measures (Hamilton scale, GAS, and Beck inventory) for the two study groups; two-tailed t tests were used.

Finally, analyses of covariance (ANCOVA) (covariate=age) with repeated measures for time were performed by comparing the more and less severe groups on the Hamilton scale, GAS, and Beck inventory across the 16-week protocol. When significant main effects or interactions (Severity Group by Time) were observed, Student-Newman-Keuls tests were planned to further examine the difference between groups or across time points. With a total of 59 patients (and harmonic mean cell sizes of N=27 patients), the planned parametric analyses had 80% statistical power to detect effect sizes of $d=0.45$ (alpha=0.05, two-tailed test) (10). This meant that we had the ability to detect in a reliable manner between-group differences of 3 points on the Hamilton scale and about 4.5 points on the Beck inventory at posttreatment or, alternatively, to detect a between-group difference of about 15% in change in scores. Thus, we considered the size of the study group to be sufficient to evaluate our hypothesis that more severely depressed patients would respond to cognitive behavior therapy as well as less severely depressed patients.

## RESULTS

Pretreatment scores on both the Hamilton scale and Beck inventory did not correlate significantly with end-of-treatment scores on these measures (r=0.13 and 0.15, respectively, df=57, $p \geq 0.20$). By contrast, a weak but statistically significant correlation was found between pre- and posttreatment GAS scores (r=0.27, df=57, p=0.04).

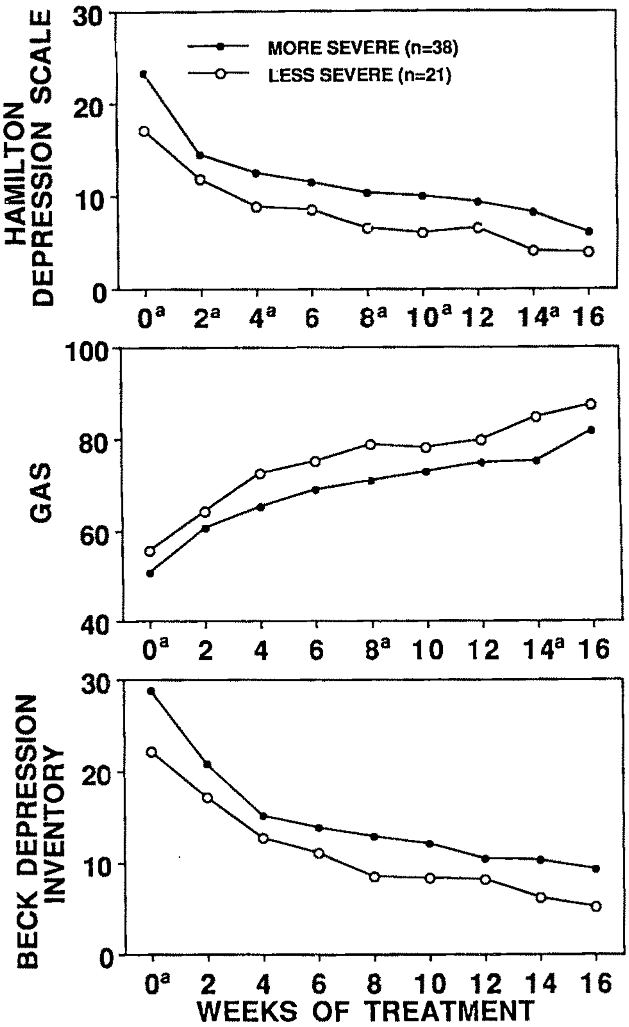
A total of 42 patients (71%) scored 6 or less on the Hamilton scale at posttreatment, and 36 patients (61%) scored 9 or less on the Beck inventory. As summarized in table 2, significantly fewer patients in the more severe group met the treatment response criteria of the Beck inventory. In addition, fewer patients in the more severe group had final Hamilton scale scores of 6 or less; however, this difference was not statistically significant (p=0.15).

Patients who were subsequently classified as nonresponders on the Hamilton scale were significantly more symptomatic, according to pretreatment GAS scores, than responders (mean±SD scores=49.1±6.9 versus 53.7±8.1; t=2.0, df=57, p=0.05). The patients classified as treatment responders on the Hamilton scale did not differ on pretreatment assessments on either the Hamilton scale or the Beck inventory. Responders according to Beck inventory criteria were significantly less symptomatic at pretreatment than nonresponders on both the Hamilton scale (scores=20.2±3.9 versus 22.4±3.8; t=2.1, df=57, p=0.04) and the GAS (54.8±7.7 versus 48.6±6.9; t=3.1, df=57, $p<0.01$). Pretreatment Beck inventory scores did not differentiate between patients classified as responders according to either the Hamilton scale or the Beck inventory.

Symptomatic status at the end of treatment, as reflected by mean end-point scores on the Hamilton scale, GAS, and Beck inventory, did not significantly differ between groups (table 2). However, in each case, the less severe group manifested less pathological mean scores. The percent change in scores, which reflects change relative to pretreatment status, did not significantly differ between the more and less severe groups (table 2).

Across the 16-week protocol, Hamilton scale, GAS, and Beck inventory scores improved significantly (according to ANCOVA) in both groups (figure 1; F=70.6, 66.5, and 66.5, respectively, df=8, 456, all p values $<0.0001$). Significant main effects for severity group also were found on all three measures (Hamilton scale: F=7.4, df=1, 56, p=0.009; GAS: F=4.7, df=1, 56, p=0.03; Beck inventory: F=4.0, df=1, 56, p=0.05). However, there were no significant interactions between severity classification and time.

FIGURE 1. Test Scores Over 16 Weeks for 59 Depressed Patients Treated With Cognitive Behavior Therapy



[a]Significant between-group differences (Student-Newman-Keuls tests).

Because the groups appeared to improve at relatively parallel rates, the ANCOVAs were repeated after covarying for week 0 (pretreatment) severity on each dependent measure. This permitted a reexamination of the between-group effects after taking into account initial differences in severity. The results of the repeat analyses indicated that the more and less severe groups did not differ significantly in subsequent outcome on any of the dependent measures after the pretreatment differences were controlled (ANCOVA group effects; Hamilton scale: F=0.13, df=1, 55, p=0.72; GAS: F=0.97, df=1, 55, p=0.33; Beck inventory: F=0.50, df=1, 55, p=0.48).

## DISCUSSION

We found some further evidence of a relationship between pretreatment severity of depression and poorer response to cognitive behavior therapy. However, the findings were not consistent across outcome indicators and appeared dependent upon which method of analysis was used. For example, several outcome classifications based on absolute score values (i.e., responder versus nonresponder comparisons, the proportion of patients who met arbitrary response criteria, and the analysis of variance main effect for severity group) indicated that the more severe group had a less complete response to treatment. The major difference between severity groups was reflected in the repeated-measures analysis of assessment scores across the course of treatment. These between-group differences were negated when level of pretreatment severity was covaried. Further, analyses based on rates of change or relative differences (i.e., percent change in scores or the ANCOVA interaction term) showed the groups to have equivalent responses. In essence, the more severe group experienced a rate of symptom reduction during cognitive behavior therapy that was comparable to the rate for the less severe patients, although the former group did not fully make up for the difference in pretreatment symptoms. We therefore conclude that we have only partially replicated an association between severity of depression and poorer response to cognitive behavior therapy.

Are the differences in outcome of the more and less severely depressed patients clinically significant? At one level, our findings do not support the notion that a simple severity criterion, such as a Hamilton scale score of 20 or more, can be used to identify patients who respond poorly to cognitive behavior therapy and thus should be treated with an alternative modality, such as pharmacotherapy. The outcome of the more severe group in this study is quite typical of depressed patients treated with a variety of active therapies, including antidepressant medications. Indeed, high pretreatment severity ratings also have been associated with poorer response to pharmacotherapy in some studies (11). This phenomenon may simply reflect a decline in response to placebo as severity of depression increases, with a relatively constant difference between drug and placebo. And yet, the fact that our more severely depressed patients did manifest higher residual scores at termination of therapy certainly suggests that their recovery was less complete. The finding of higher residual depressive severity alone may convey a higher risk for subsequent relapse (12, 13). Although a combined psychotherapy/pharmacotherapy regimen might reduce such a risk (14), so might a longer or more intense course of cognitive behavior therapy (13).

Our findings differ from those of the Collaborative Research Program (4) in several respects. First, the overall response to cognitive behavior therapy in the total patient group was greater in our study (e.g., Hamilton scale score of 6 or less: our study=42 of 59 patients [71%], Collaborative Research Program=20 of 50 patients [40%]; $\chi^2=10.7$, df=1, $p<0.001$). Second, the relative responsiveness of the more severely depressed subgroup was higher in our study. Several factors might have accounted for the difference in results. In the absence of placebo- and tricyclic-treated comparison groups, it is impossible to gauge the inherent potential for positive outcome of this subgroup. Further, patients in the present study were treated in a specialty clinic devoted to research using cognitive behavior therapy, whereas patients in the collaborative study were randomly assigned to treatment in a clinic that was not committed to a particular type of therapy. Treatment response rates are generally higher in "open-label" trials (11). Other differences might include our exclusion of patients with RDC diagnoses of nonendogenous depression, the inclusion of more chronically depressed patients in the collaborative study, or subtle differences in therapist competence. We hope to examine these possibilities, as well as other explanations, in collaboration with our colleagues from the Pittsburgh component of the Collaborative Research Program.

Until such data are forthcoming, we propose that the combination of ongoing, weekly therapy supervision and the provision of treatment in a specialty clinic milieu made the critical difference in treating more severely depressed patients in the present study. The weekly supervision received by the therapists in the present study may be particularly salient, since Shaw (15) has noted that patient difficulty may adversely affect the technical quality of cognitive behavior therapy. Thus, therapists may require more intensive supervision in order to maintain optimal cognitive behavior therapy with more severely depressed patients. Alternatively, the esprit de corps of a specialty clinic may help the therapist and patient to continue to engage in therapy until a more severe depressive episode begins to remit, despite a somewhat slower course of recovery. The latter explanation touches on a clinically relevant variant of experimental bias, in which both the therapists' and patients' expectations of positive outcome may influence the subsequent response rate.

In summary, our findings suggest that in an open treatment setting, cognitive behavior therapy is nearly as effective a treatment of moderately severe depression (i.e., Hamilton scale scores of 20–25) as it is in milder depression. Nevertheless, more severely depressed patients did finish treatment with somewhat less complete remissions and might benefit from longer or more intensive courses of therapy. The efficacy of cognitive behavior therapy in even more severely depressed patients (e.g., inpatients or melancholic outpatients with Hamilton scale scores greater than 25), of course, remains to be determined.

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# Elevation of Plasma Concentrations of Haloperidol After the Addition of Fluoxetine

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*Fluoxetine (20 mg/day) was added for 7–10 days to stable doses of haloperidol given to eight psychotic patients. Mean plasma concentrations of haloperidol were elevated by 20% ($p<0.05$), but extrapyramidal side effects did not increase appreciably, indicating a relatively minor interaction between these agents.*

(Am J Psychiatry 1991; 148:790–792)

Fluoxetine, a selective blocker of neuronal uptake of serotonin, can increase blood concentrations of tricyclic antidepressants (1) and diazepam (2), probably by competitive inhibition of hepatic metabolism (1). The possibility that fluoxetine may affect tissue concentrations of antipsychotic drugs is suggested by observations that fluoxetine added to neuroleptics improved antipsychotic response in schizophrenic patients (3) and increased extrapyramidal symptoms (1). To determine whether fluoxetine alters availability of haloperidol, we measured plasma concentrations of haloperidol in patients given fluoxetine in addition to stable doses of haloperidol; extrapyramidal signs also were rated.

## METHOD

The subjects were eight outpatients (two women and six men), ages 29 to 56 years (mean=38), who had taken a stable daily oral dose of haloperidol (average=14 mg/day) in tablet form for at least 3 months before the study. All patients gave informed consent. Diagnoses, based on the Structured Clinical Interview for DSM-III-R (SCID), were schizophrenia (seven patients) and schizoaffective disorder (depressed) (one patient). Fluoxetine, 20 mg/day, was added for 10 days; there were no other medication changes.

Patients were examined for extrapyramidal symptoms by a research psychiatrist, using the Simpson-Angus Scale (4), at baseline and 7–10 days after fluoxetine treatment was begun. Blood was drawn after each rating was completed, a mean±SD of 14.6±2.3 hours after the last dose of haloperidol (±30 minutes within subjects). Plasma was separated within 15 minutes and stored at −30 °C until it was assayed under blind conditions for haloperidol and reduced haloperidol. The high-performance liquid chromatography procedure (5) is sensitive to 50 pg/ml of haloperidol with a coefficient of variation no greater than ±7%. Accuracy was greater than 85% for samples to which authentic analytes were added. Adding fluoxetine did not interfere with the assay. Data are presented as means±SD unless otherwise stated.

## RESULTS

All eight patients completed the study with haloperidol doses of 13.6±12.0 mg/day and a mean baseline haloperidol concentration of 8.3±8.5 ng/ml (reduced

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**TABLE 1. Plasma Haloperidol Levels and Extrapyramidal Symptom Scores of Eight Psychotic Patients Before and During Addition of Fluoxetine**

| Subject | Sex | Age (years) | Haloperidol Dose (mg/day) | Haloperidol Level (ng/ml) Baseline | Fluoxetine[a] | % Change | Extrapyramidal Symptom Score[b] Baseline | Fluoxetine[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | M | 29 | 5 | 0.1 | 2.1 | +2300 | 2 | 2 |
| 2 | F | 31 | 4 | 1.1 | 2.0 | +82 | 0 | 0 |
| 3 | M | 40 | 10 | 2.0 | 7.4 | +272 | 2 | 2 |
| 4 | M | 39 | 15 | 4.5 | 5.5 | +21 | 0 | 0 |
| 5 | M | 35 | 20 | 6.8 | 6.8 | +1 | 1 | 2 |
| 6 | M | 47 | 10 | 12.8 | 15.6 | +22 | 5 | 6 |
| 7 | F | 56 | 5 | 13.5 | 15.4 | +14 | 2 | 2 |
| 8 | M | 29 | 40 | 25.3 | 24.4 | −3 | 1 | 0 |

[a] 20 mg/day.
[b] According to Simpson-Angus Scale (4).

haloperidol=3.8±7.0 ng/ml). Seven to 10 days after fluoxetine was added, the mean plasma haloperidol concentration had increased significantly—by 19.9%—to 9.9±7.9 ng/ml ($t=2.43$, all $df=7$, $p<0.05$, paired two-tailed t test), with an increase in seven of the eight patients (table 1). When the data from patient 1 (23-fold increase) were removed, the mean elevation in the other seven patients was 16% ($t=2.05$, $p=0.09$). No patient achieved a level of haloperidol during fluoxetine treatment that was greater than the highest baseline level (25.3 ng/ml). Neuroleptic levels before and during fluoxetine treatment were strongly correlated ($r=0.98$, $p<0.001$); there was a significant correlation between dose and baseline plasma concentration of haloperidol ($r=0.75$, $p<0.04$). Plasma concentrations of reduced haloperidol also tended to increase (by 26%) after the addition of fluoxetine ($t=1.47$, $p>0.05$), and the ratio of reduced haloperidol to haloperidol in plasma increased by 35% after the addition of fluoxetine (0.26 to 0.35; $t=2.61$, $p<0.05$).

Mean extrapyramidal symptom scores did not change significantly after the addition of fluoxetine (1.6±1.6 versus 1.8±2.0); only two patients scored higher on any item. One (patient 5) developed mild akathisia, and another (patient 6) developed mild tremor.

## DISCUSSION

The 20% elevation in plasma levels of haloperidol 7 to 10 days after the addition of a typical daily dose of fluoxetine (20 mg) to a stable oral daily dose of haloperidol (mean=14 mg) generally is consistent with reports of fluoxetine-induced elevation of plasma levels of tricyclic antidepressants (1) and diazepam (2). While great individual variability was evident, five of eight patients had substantial (greater than 20%) increases in plasma levels of haloperidol (table 1). Some variability may reflect imperfect compliance with treatment, although all patients were in residential programs with closely supervised medication.

The addition of fluoxetine was associated with minimal clinically significant increases in extrapyramidal symptom ratings. We expected to find worsening of extrapyramidal symptoms both as a result of a predicted pharmacokinetic interaction between fluoxetine and haloperidol, resulting in elevated haloperidol levels, and as a result of fluoxetine's indirect inhibition of dopamine synthesis. Serotonergic systems can inhibit dopaminergic projections from the midbrain (6, 7), and this effect may contribute to neurological actions of fluoxetine such as akathisia (8) and its reported interactions with neuroleptics (6, 9).

On the basis of the total of 20 patients from this and another study (3), the prevalence of clinically significant worsening of extrapyramidal symptoms after the addition of fluoxetine to neuroleptic treatment may be as low as 5%. Most of the risk appears to occur early in neuroleptic therapy (1). A greater risk for extrapyramidal symptoms with this combination early in the course of antipsychotic treatment may reflect the greater modulating effect of serotonin on dopamine activity elevated above baseline levels (7), a characteristic of the early phase of neuroleptic treatment (10).

Clinicians who choose to add fluoxetine to haloperidol or other antipsychotic agents should be aware that, although the combination may benefit some psychotic patients, fluoxetine may elevate neuroleptic levels in some patients, at least moderately. Extrapyramidal symptoms may worsen in part on this basis if neuroleptic levels are close to an "extrapyramidal symptoms threshold" before the addition of fluoxetine or through interactions between central serotonergic and dopaminergic systems. Akathisia may be especially likely to develop when fluoxetine is added early in neuroleptic treatment. The report of enhanced antipsychotic efficacy after the adjunctive use of fluoxetine (3) needs to be interpreted in the light of the moderate pharmacokinetic interaction reported here. We suggest that potential complications or therapeutic advantages of the combination of fluoxetine with neuroleptics deserve further clarification.

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# Nicotine Potentiation of Haloperidol in Reducing Tic Frequency in Tourette's Disorder

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*In an open, nonblind study, 10 patients with Tourette's disorder who were being treated with haloperidol were videotaped before, while, and after chewing nicotine gum. The frequency of tics was reduced significantly during the 30-minute gum-chewing period and during the 1 hour after gum chewing. Nicotine appears to potentiate haloperidol effects in patients with Tourette's disorder.*

(Am J Psychiatry 1991; 148:793–794)

Tourette's disorder is most frequently treated with neuroleptic medication, especially the dopamine antagonist haloperidol, which is effective in about 70% of the cases (1, 2). However, haloperidol has frequent side effects—including difficulty in concentration, drowsiness, weight gain, and attentional problems—which often affect compliance (3).

We demonstrated (4) that in animals low doses of nicotine potentiated the cataleptic effects of haloperidol by approximately 10-fold. This in turn suggested that reduction of motor activity might be observed after similar coadministration of nicotine to patients with a neuroleptic-responsive movement disorder, such as Tourette's disorder. We found reduction in tic frequency in an initial open study with two Tourette's disorder patients (5) and in a further open study with 10 Tourette's patients in which symptoms were reported by both the parents and the children (6).

In this paper, we report the effects of chewing one piece of nicotine gum (containing 2 mg of nicotine) on tic frequency in 10 patients whose Tourette's disorder was inadequately controlled by haloperidol, either because of unsatisfactory clinical response or excessive side effects. In this study, the tic frequency change was assessed directly by clinicians.

## METHOD

The patients were eight children and two adults; nine were male and one was female. They ranged in age from 8 to 46 years; the mean age was 18.7, and the median was 16 years. Their mean score on the Yale Global Tic Severity Scale (7) was 66 1, and the median was 61.5. On the 7-point Clinical Global Impression Scale for Tourette Syndrome (8) the mean score was 4.6, and the median score was 4.0. The mean duration of symptoms was 85.8 months, and the median was 42.0 months. Haloperidol had been used by the patients at a mean dose of 2.8 mg/day; the median was 1.25 mg/day.

All of the subjects gave informed consent for the procedure, which was an open study in which each patient served as his or her own control. The same two raters performed all of the ratings on each individual patient. Each subject was videotaped over a 2-hour period, during quiet conversation between the patient and the examiner. Such conversation deliberately avoided topics of known stress. All patients had been taking haloperidol for at least 1 month before nicotine administration.

An initial 30-minute period indicated the baseline frequency of individual motor and vocal tics and, therefore, total tics. The child or adult was then immediately given one piece of nicotine polacrilex to chew over 30 minutes, according to the standard instructions given by the manufacturer (*Physician's Desk Reference*, 1990). A placebo-controlled design was not

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**TABLE 1. Total Tic Frequency for Patients With Tourette's Disorder Before, During, and After Nicotine Gum Chewing**

| | Number of Tics During 30-Minute Period | | | |
|---|---|---|---|---|
| | | | After End of Chewing | |
| Patient | Baseline | Gum Chewing | 0–30 Minutes | 30–60 Minutes |
| 1 | 249 | 108 | 93 | 59 |
| 2 | 1095 | 593 | 600 | 861 |
| 3 | 83 | 27 | 32 | 61 |
| 4 | 569 | 363 | 342 | 312 |
| 5 | 368 | 141 | 167 | 180 |
| 6 | 326 | 134 | 144 | 158 |
| 7 | 324 | 126 | 312 | 260 |
| 8 | 95 | 41 | 63 | 71 |
| 9 | 413 | 365 | 282 | 321 |
| 10 | 332 | 293 | 525 | 455 |

used in this initial open study, because a placebo gum that tasted similar to the active gum was not available at the time of this study. All patients kept the gum in their mouths throughout the full 30-minute period of gum chewing. The gum was then removed from the mouth, and two consecutive 30-minute postgum assessment periods followed.

After an initial 5-minute survey of the tapes, the types and frequencies of simple and complex motor and vocal tics were agreed on by consensus after discussion. The videotapes of each 2-hour session were then assessed for total tic frequency by two independent raters; these ratings were done in 2-minute segments because of the complexity of rating numerous tics over time. The same two raters did all the ratings on each individual patient. The interrater reliability for 30-minute total tic frequency over the four conditions—before-gum baseline, gum chewing, and first and second after-gum periods—was estimated for six cases with the intraclass correlation coefficient (ICC) (9). Adequate interrater agreement was obtained ($ICC=0.95$, $p<0.01$).

## RESULTS

Table 1 shows the total tic frequencies during the four 30-minute periods for each of the 10 subjects. Compared to baseline, patients 1–9 had a lower tic frequency during the gum-chewing period and both after-gum periods. Patient 10 had a lower tic frequency only during the gum-chewing period and had increases in the two after-gum periods.

The mean 30-minute tic frequencies for the 10 patients over the four conditions were 385.4, 219.1, 256.0, and 273.8, respectively. A one-within (repeated measures) analysis of variance tested for differences in mean tic frequency among the four conditions. Significant differences between means were found by this procedure ($F=6.57$, $df=3, 27$, $p<0.01$). Follow-up comparisons between conditions showed significant reductions in total tic frequency between the baseline and gum-chewing periods ($F=14.20$, $df=1, 9$, $p<0.005$), between the baseline and 0–30-minute after-gum periods ($F=5.29$, $df=1, 9$, $p<0.05$), and between the baseline and 30–60-minute after-gum periods ($F=8.99$, $df=1, 9$, $p<0.05$).

## DISCUSSION

These results indicate a marked potentiation of haloperidol effects by nicotine gum in diminishing tic frequency in Tourette's disorder. In part these results agree with the findings in our animal studies (4). This dramatic response occurred approximately 3 minutes after the subject began chewing a single piece of nicotine gum containing 2 mg of nicotine; the mechanism by which this occurs is not currently known. It is interesting that a recent communication (10) described beneficial effects of cigarette smoking in a Tourette syndrome patient who had previously taken neuroleptics. It may be that the dopamine antagonist effect of haloperidol initially increases the activity of cholinergic neurons in the striatum and that nicotine subsequently acts as an additional agonist on nicotinic cholinergic receptors, thereby increasing catalepsy in animals and decreasing tic frequency in patients with Tourette's disorder. A number of further clinical and animal experiments are currently under way by our group. Obviously we do not recommend the uncritical and excessive use of nicotine polacrilex as an adjuvant to haloperidol in treating Tourette's disorder, but the initial responses to modest doses are extremely encouraging.

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# Vulnerability to Sodium Lactate in Panic Disorder Patients Given Cognitive-Behavioral Therapy

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*Six patients with panic disorder who had panicked during sodium lactate infusion were given cognitive-behavioral treatment for 12–24 weeks. After treatment they underwent another lactate infusion, and four patients were rated as having no panic, suggesting that reduced vulnerability to lactate accompanies remission of panic. Controlled trials of cognitive-behavioral therapy and use of lactate infusion as a measure of remission are recommended.*

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Patients with panic disorder often experience a panic episode when given an infusion of intravenous sodium lactate (1). Lactate-provoked panic attacks are described by patients as very similar to naturally occurring episodes. Lactate panic is usually blocked when effective clinical remission is achieved with tricyclic antidepressant medication (2), but pretreatment with β blockers, known to be relatively ineffective in treating panic patients, does not affect vulnerability to lactate (3).

Cognitive-behavioral techniques that appear to alleviate panic attacks have now been developed (4). We report here a pilot investigation designed to obtain preliminary data about lactate response in patients who are panic free after cognitive-behavioral treatment. In this uncontrolled pilot study, neither clinical remission nor change in responsiveness to sodium lactate can necessarily be attributed to specific treatment effects. With this caveat in mind, we report posttreatment results of sodium lactate testing in six patients who had pretreatment lactate panic attacks.

## METHOD

The subjects met the *DSM-III-R* criteria for panic disorder with mild or moderate agoraphobia. Diagnosis was made by separate clinical evaluations by the first and second authors and confirmed with semistructured assessment instruments: the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (Modified for the Study of Anxiety Disorders) (5) and the Structured Clinical Interview for DSM-III (6). The six subjects reported on in this article were part of a larger sample of 20 outpatients who gave informed consent to undergo sodium lactate testing followed by cognitive-behavioral treatment and posttreatment reinfusion. The six patients represent the subgroup who 1) developed panic attacks during pretreatment sodium lactate infusion, 2) became panic free during cognitive-behavioral treatment, and 3) consented to undergo repeat infusions.

All patients were free of other current *DSM-III* axis I diagnoses and free of medical illness. All patients had been free of medication for at least 3 days prior to sodium lactate testing, both before and after treatment.

Sodium lactate testing was done according to standard procedures that have been described previously (2). Patients received a 30-minute infusion of normal saline followed by 0.5 M sodium lactate, 20 mg/kg, infused over 20 minutes. Patients knew they would receive lactate at some point but did not know when the change was made. Specific symptoms were monitored at regular intervals during the infusions with a standardized scale called the Acute Panic Inventory (available from the first author on request). Outcome was rated categorically by an observing physician as "panic" or "no panic." Criteria for a panic episode included both the report of a crescendo to extreme apprehension or fear and the presence of at least four of the *DSM-III* physical symptoms. The physician

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**TABLE 1. Data on Six Patients With Panic Disorder Who Underwent Lactate Infusions Before and After Treatment**

| Patient Number | Age (years) | Sex | Duration of Illness (years) | GAS Score[a] Before Treatment | GAS Score[a] After Treatment | CGI Score[b] Before Treatment | CGI Score[b] After Treatment | Panic Status[c] Before Treatment | Panic Status[c] After Treatment | Response to Lactate Before Treatment | Response to Lactate After Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 37 | F | 10 | 38 | 70 | 4 | 2 | 1 | 4 | Panic | No panic |
| 2 | 34 | M | 12 | 60 | 80 | 4 | 1 | 3 | 1 | Panic | No panic |
| 3 | 28 | F | 6 | 55 | 65 | 5 | 4 | 4 | 3 | Panic | Panic |
| 4 | 17 | F | 1 | 50 | 58 | 5 | 3 | 4 | 3 | Panic | No panic |
| 5 | 33 | F | 1 | 60 | 70 | 4 | 3 | 4 | 1 | Panic | No panic |
| 6 | 23 | F | 3 | 61 | 90 | 4 | 1 | 4 | 3 | Panic | No panic |

[a] GAS=Global Assessment Scale: functional impairment as rated on *DSM-III-R* axis IV; higher scores indicate better functioning.
[b] CGI=Clinical Global Impression: a measure of severity of illness, where 1=no illness, 2=borderline, 3=mild, 4=moderate, 5=marked, 6=severe.
[c] 1=no full-blown or limited-symptom episodes in the month before rating; 2=no full and less than four limited-symptom episodes per month; 3=no full and more than four limited-symptom episodes per month; 4=one or more full-blown panic episodes per month.

rater was blind to the patients' diagnoses and treatment status.

Cognitive-behavioral treatment included presentation of a model of panic, instruction in techniques of slow abdominal breathing, deep muscle relaxation, and a program of exposure to internal and external panic-provoking stimuli. Duration of treatment was 24 weeks for four patients, 18 weeks for one, and 12 weeks for one. We rated clinical panic status, before and after treatment, for a month before the lactate infusions. These ratings were based on an interview about panic attack frequency that was conducted by a rater blind to the patient's lactate responses.

## RESULTS

Twelve of the original 20 patients experienced pretreatment lactate-induced panic. Nine of these improved and three did not improve with treatment. Two of the nonresponders dropped out before the third treatment session. Six patients consented to posttreatment infusions. Clinical status and lactate outcome for these patients are summarized in table 1.

Four patients (patients 2, 4, 5, and 6) were rated by themselves and the blind rater as having no panic on repeat lactate infusion. Two of these (patients 2 and 5) had no posttreatment panic at all, and two (patients 4 and 6) had residual limited-symptom episodes.

One patient (patient 1) had a panic attack after 18 minutes of the repeat lactate infusion. Her pretreatment panic had occurred 8 minutes into the infusion. She reported feeling fine during most of the posttreatment infusion. At a debriefing interview conducted by her therapist, she reported that just prior to her panic episode, she thought she had noticed a sudden increase in the frequency of the rater's questions and concluded she was in physical danger. This patient had been panic free after treatment. However, she experienced a full-blown panic episode in the time between termination of treatment and the second lactate infusion. Her avoidance behavior and anticipatory anxiety had been considerably less after treatment. Her overall improvement was reflected in a 32-point improvement on the Global Assessment Scale (7) and a rating of very much improved on the Clinical Global Impression scale, and we decided to include her in the posttreatment testing group. We changed her posttreatment panic rating after she experienced the panic episode. None of the other five patients experienced a panic episode in the interim period.

The sixth patient (patient 3) asked to terminate the infusion at 11 minutes (9 minutes early). This patient had panicked after 6 minutes of the pretreatment infusion. Her posttreatment clinical panic rating was 3. At the second infusion she did not feel she had experienced a panic episode, but she made a decision to terminate the infusion because the physical symptoms were uncomfortable. However, the physician rated her as having had a panic episode. At a debriefing interview, the patient again explained that she believed her request to terminate the infusion early did not occur because of a panic episode. She attributed her request to an increase in assertiveness. She also reported that her husband had strongly advised her not to undergo the repeat infusion because he felt she could be damaged by the "chemicals." Nevertheless, following usual procedures, we rated this patient as having posttreatment lactate-induced panic.

In summary, the four patients who did not panic during the posttreatment lactate infusion were clinically free of full-blown panic symptoms after treatment. Two had residual limited-symptom episodes. One patient who panicked during posttreatment infusion had had two full panic attacks during the month prior to reinfusion. The second patient rated by us as having posttreatment panic had had only limited-symptom episodes in the month prior to reinfusion.

## DISCUSSION

In this pilot study we observed reversal of vulnerability to lactate in four of six patients treated with cognitive-behavioral therapy, as did Guttmacher (8) in a single patient. The most likely explanation for these findings is that patients in clinical remission from panic disorder show diminished sensitivity to sodium lactate infusion. The issue of what interventions induce remission is not fully understood.

One possibility is that the cognitive-behavioral treatment we used had specific antipanic effects. It is also possible that spontaneous remission of panic may occur in the course of treatment, or remission may have occurred in response to nonspecific factors such as presentation of a model for panic and a credible treatment rationale, expectation of success, or imparting to the patient a sense of control.

It is possible that patients become desensitized to lactate on repeat infusions (9) or that our results occurred by chance because of the small number of subjects. Our patients underwent only two infusion procedures, and although there are no systematic test-retest data available, previous work suggests that patients undergoing two pretreatment lactate infusions regularly panic at the second as well as the first procedure (3).

Another possibility is that patients treated with cognitive-behavioral therapy continue to have autonomic symptoms of panic but interpret these symptoms differently. During treatment they may have learned less frightening ways of interpreting sensations or different expectations of the consequences of noticeable bodily sensations. This explanation would be consistent with studies suggesting that the instructional set may influence responses to pharmacologic testing (10–12). However, the definition of panic was vague in each of these studies.

In conclusion, we found a high rate of reversal of vulnerability to lactate in this pilot study of six patients with panic disorder treated with cognitive-behavioral therapy. The most likely explanation for our findings is that the reversal of lactate response correlates with clinical remission. More work is needed to describe better the specific effects of cognitive-behavioral techniques, to elucidate the mechanism of changes in lactate responsiveness, and to compare effects of cognitive-behavioral and medication treatments.

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# Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

## NOSOLOGY

**Contemporary Themes in Psychiatry: A Tribute to Sir Martin Roth,** *edited by Kenneth Davison and Alan Kerr. London, Gaskell (Royal College of Psychiatrists), 1989, 506 pp., £20.00 (paper).*

There have been fundamental changes in psychiatry in the United States over the past 20 years that have involved substantial shifts in both theory and practice. Although the reasons for these changes are often attributed primarily to advances in psychopharmacology and the neurosciences, other equally important explanations exist as well. As Gerald Klerman notes in the preface to this volume, a fundamental component of this change was a paradigmatic theoretical shift that occurred in psychiatry in the early 1970s. This shift involved a reaffirmation of the concept of the existence of multiple discrete disorders and the use of operational criteria for psychiatric diagnoses based on categorical case assignment. This transition was consolidated by the introduction and publication of the DSM-III system of psychiatric nosology in the early 1980s. Although the introduction of DSM-III caused some degree of controversy, there is now general consensus that the document facilitated bringing organization and clarity into standardizing clinical diagnoses. This standardization formed a basic rubric for subsequent biological research and systematic testing of psychotherapeutic and somatic treatment modalities.

The theoretical framework for the *DSM-III* system can be traced historically to the British neo-Kraepelinian school of investigators best represented by Mayer-Gross, Slater, and Sir Martin Roth, the honoree of this book. Martin Roth, in particular, has had a rather marked effect on U.S. psychiatry through three major contributions: 1) the use of multivariate statistical techniques for the analysis of psychopathological symptoms, 2) the measurement of treatment response to tricyclic antidepressants and ECT to validate diagnostic distinctions between syndromes, and 3) facilitating the renaissance of the classic Kraepelinian approach to diagnosis, emphasizing discrete rather than continuous-spectrum psychopathological states. These approaches are now part of the established model of clinical practice and research in the United States, but they represent a profound evolution from the psychiatry of 20 years ago. Efforts to better define psychiatric disorders in respect to their epidemiology, course, and response to treatment have been most visibly fostered in the United States by the efforts of researchers at Washington University in St. Louis and at the University of Iowa.

This book, which consists of invited contributions by individuals who have either worked directly with or been heavily influenced by Sir Martin Roth, presents an impressive spectrum that includes chapters on techniques of descriptive psychiatric research, geriatric psychiatry, neuropsychiatry, psychosurgery, neuro-ethology, clinical epidemiology, electroencephalography, neuroimaging techniques, psychiatric historiography, the relationship between neurophysiology and Jungian psychology, and even a chapter on the psychological case history of a cold war spy. What is remarkable about this collection is that one individual could have influenced such a disparate group of contributors.

In respect to specific content, the strongest sections of the text are those which cover the evaluation of psychometric techniques to delineate subtypes of depression and the section on disorders of the elderly (both major focuses of Martin Roth's research). The latter section includes contributions on the phenomenology of paraphrenia as well as neuroimaging techniques and the neuropathology of dementia. Other, smaller gems can be found in the text, such as the overview chapters by Melvin Sabshin, Gerald Klerman, and Daniel X. Freedman, which present theoretical and historical perspectives of the development of modern psychiatry. A primary value of the text, however, beyond the quality of its individual contributions, is that it historically documents the contributions of Martin Roth to psychiatry, providing a benchmark by which to measure the field's further scientific evolution.

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**The Validity of Psychiatric Diagnosis,** *edited by Lee N. Robins and James E. Barrett. New York, Raven Press, 1989, 350 pp., $90.00.*

> A method of achieving diagnostic validity in psychiatric illness is described, consisting of five phases: clinical description, laboratory study, exclusion of other disorders, follow-up study, and family study. (1)

About 20 years ago, a Midwestern version of *perestroika* began reshaping the landscape of U.S. psychiatry. *The Validity of Psychiatric Diagnosis* critically examines the current legacy of these changes in order to understand how far the process has come and to map out a course for the future. The quote at the beginning of this review is abstracted from a paper (1) (reprinted in full at the beginning of the book) that the editors believe marks the beginning of this *perestroika.* Indeed, many of us who completed psychiatric residencies in the 1970s viewed this statement as a prescription for opening the process of psychiatric diagnosis to the light of empirical hypothesis testing.

The historical significance of the content of this book is reinforced by the historical importance of the chapter authors themselves, including Bruce Dohrenwend, Joseph Fleiss, Elliot Gershon, Sam Guze, Robert Kendell, Eli Robins, Lee Robins, and Robert Spitzer as well as a number of second-generation empiricists whose publications have not yet turned sufficiently yellow to be considered historical. In addition to the formal presentations, each chapter ends with a transcription of the question-and-answer sessions that followed each talk. These exchanges involving the movers and shakers of empirical psychiatry are no less illuminating than the formal presentations.

Productive *perestroika* must always include *glasnost,* and this book does a credible job of openly critiquing the effects of the validity-testing approach to diagnosis. Dr. Cloninger's chapter notes the proliferation of alternative criteria sets as evidence for the difficulty of developing one diagnostic system that is valid for all purposes when a clearly etiologically based system of diagnosis is not yet possible. Dr. Blashfield's chapter extends this line of thought by considering the consequences of trying to improve reliability and validity with a diagnostic system that purports to be atheoretical.

Dr. Dohrenwend and Dr. Lee Robins, along with others, review the strengths and limitations of what must be considered the strategic warhead of empirical psychiatric diagnosis: the structured diagnostic interview. Both acknowledge that there are problems in applying these instruments to general population studies. Dr. Robins defends current levels of precision by stating, "Perhaps one should not expect agreements between psychiatric assessments to surpass those for other assessments in medicine . . . [such as] between various methods of suspecting breast cancer and biopsy results" (p. 267). The problem remains that there are few useful biopsy procedures in psychiatry.

Several of the chapters deal with statistical procedures for addressing such difficult issues as when to "lump" different syndromes with much in common and when to "split" syndromes with apparently distinct subtypes. Samplings of longitudinal follow-up studies, laboratory studies, genetic studies, and pharmacological trials are examined in separate chapters with the goal of evaluating how far we have come in establishing valid diagnostic entities.

A careful reading of the material in this book will serve to caution the investigator against having too much confidence that the current diagnostic schemes are truly "carving nature at the joints." The book makes it clear that the various criteria for validation proposed by Robins and Guze are not yet converging on a single unified approach to psychiatric diagnosis. On the other hand, one is left with the conclusion that the operational approach to diagnosis and validity testing allows future investigators to build on the foundation of past findings in a way that was not previously possible. Just as the production of goods must not be sheltered from the reality of market forces, psychiatric theories must not be sheltered from the reality of scientifically sound empirical studies.

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**Life Events and Psychiatric Disorders: Controversial Issues,** *edited by Heinz Katschnig. New York, Cambridge University Press, 1987, 265 pp., $52.50.*

The title of this volume describes its contents well. The eight contributors have tackled the issues that complicate life events research and thereby provide a comprehensive evaluation of the status of that research and its future prospects. The various topics have been carefully selected and arranged. The first chapter, Brian Cooper's "Mental Disorder as Reaction: The History of a Psychiatric Concept," supplies a scholarly background for the discussions of theory, research strategies, and differing viewpoints that follow. Cooper emphasizes that at least since the days of Pinel, Esquirol, and the usually overlooked Griesinger, mental illness has been considered to be the result of a combination of numerous predisposing and exciting causes. Cooper's examination of current concepts of mental disorder is impressive.

In chapter two, Turpin and Lader discuss biological mechanisms and present specific models of interactions between stress and vulnerability for anxiety, depression, and schizophrenia. They note, however, that there is little empirical support for the models and specify five areas for future research: 1) biological changes in normal populations that occur as a consequence of life events, 2) the separation of state-trait interaction by prospective studies, 3) the measurement of chronic difficulties and minor life events, 4) the mechanisms responsible for the interaction between stress and vulnerability, and 5) moderating social factors.

In chapter three, Becker discusses psychological mechanisms, especially the role of life events as factors that predispose to and precipitate illness. He draws heavily on the work of Bowlby and Harlow to illustrate how such early life experiences as deprivation may interconnect with later stress situations. Becker also looks at Seligman's concept of learned helplessness and at the views of Lazarus and his colleagues regarding cognitive appraisal and the significance of these views in the still unbalanced stress-coping equation. Unfortunately, an integrated theory of the complex problem of stress, coping, and mental illness can be only dimly sketched.

In chapter four, Katschnig incisively evaluates the two major instruments used to measure life stress, Holmes and Rahe's Schedule of Recent Experience and its arbitrary life crisis units and the Life Event and Difficulty Schedule of Brown et al., which yields a stress score produced by a group of raters who consider the context in which the event occurred. Katschnig's studies show that the use of these two differing techniques in groups of depressed patients could yield identical results when only the aggregate data were considered; however, there was remarkably little congruence between the two when specific life events were evaluated in reliability studies. Such a finding epitomizes many of the major problems complicating stressful life events research. Katschnig concludes that the major discrepancies in life events research should make researchers cautious.

The chapter by Brown and Harris on causal links and on their Bedford College studies of depression is a scholarly 70-page summary of their work over the past 15–20 years. They discuss major problems with life events research systematically and describe the development of their concepts and methods during the years they worked in London and in the Hebrides. Importantly, Brown and Harris link stressful life events with ongoing difficulties. In addition, they introduce the needed concept of the "potential to produce symptoms for secondary gain" as a factor that influences the meaning or stress associated with an event.

Brown and Harris look directly at the central problem of the meaning of life events. It is often possible to obtain consensus about the general meaning of a particular event—its desirability or undesirability—but the specific meaning, what the event means to the individual, remains quite elusive. How to evaluate the meaning of a life event to a human being is, to me, the most baffling research problem in this field. An individual's either forgetting events or overestimating their number and significance is primarily a matter of meaning, what W.I. Thomas many years ago referred to as "the definition of the situation."

Brown and Harris point out the limitations of stressful life events research. In many studies, life events can explain only 10% or less of the variance. Many major problems are methodological; probably the results of almost all life events research have been complicated by problems with recall and reliability. Brown and Harris conclude their chapter, which is a small monograph, with a call for research on how coping, personality, and physiological susceptibility influence life events. They see their semistructured interview and contextual measurement as important contributions to this research.

In his chapter on causal links, Bebbington focuses mainly on depression and the ways in which life events are quantified. Repeatedly, studies have shown that respondents often either forget or magnify the number of events. The effect of illness on either the forgetting or the magnification of events is a substantial research problem that has not been solved. Bebbington pleads for an integrated approach in future life events studies that considers both biological and social factors.

In chapter seven, "Life Stress and Depressive Subtypes," Katschnig et al. discuss the confusion about depressive types and subtypes, classification, terminology, and diagnostic criteria. The imprecise use of diagnostic terms and concepts handicaps research on depression, as illustrated by the differing ways in which endogenous depression as opposed to reactive or other types of depression is understood. The authors' Vienna Study of Depression revealed that arbitrary definitions of depressive subtypes lacked validity. They also found that cluster analytic studies using phenomenological data had promise. However, they emphasize that their research on depressive subtypes is still relatively inconclusive and list four recommendations: 1) the necessity to clarify matters relating to terminology and definition, 2) the necessity to conduct data analyses at the symptom level and to use a multiaxial approach in order to supplement the categorical approach to psychiatric diagnosis and lessen its tautologies, 3) the desirability of using a polydiagnostic approach at this time, and 4) the need for more rigorous methods than those currently used in life events research.

In the final chapter, the editor outlines prospects for future research. He emphasizes the need for greater precision in the phenomenological description of mental disorders and in the measurement of life stress. Areas requiring exploration are the process of coping with life events, moderating factors, and the interplay between psychosocial and biological factors. Katschnig advocates using multiple methods of data analyses. He concludes that future controversies should focus on "specific 'life stress-vulnerability' risk constellations and specific pathogenetic processes" and exhorts researchers to overcome the obstacles produced by the age-old dichotomous view of the mind and body.

This book is highly recommended. In slightly more than 260 pages, the authors discuss the history of life events research, its immense methodological difficulties, and avenues for the development of methods that have a potential for shedding light on the seemingly obvious but baffling relationship between adversity and illness. The editor has skillfully brought together many of the foremost researchers in this field and has added his own scholarly views. The comprehensive bibliographies are especially valuable. The book will be of benefit to researchers in psychiatry, psychology, and the behavioral sciences, and it will be useful to clinicians, trainees, and young professionals who are preparing for advanced degrees or Board examinations.

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## SUICIDE

**Suicide: Understanding and Responding,** *edited by Douglas Jacobs and Herbert N. Brown. Madison, Conn., International Universities Press, 1989, 505 pp., $60.00.*

My first reaction to this book was, Not another published symposium on suicide, one promising "Harvard Medical School perspectives" yet. Surely this book would prove to be another filled with uneven editing and redundancies. What a nice surprise, therefore, to discover that I was wrong. This is a most readable work, only minimally redundant, and presents some new and some provocative material.

Beginning in 1981, Harvard Medical School has sponsored an annual symposium on suicide. By selecting and organizing the various presentations at these symposia the editors have produced a more comprehensive overview of suicide than one could expect from a single symposium. What I found particularly helpful, however, is the inclusion of a number of chapters not generally found in books on suicide, such as the sections on psychotherapeutic strategies and pitfalls, the aftermath of suicide, and philosophical perspectives on suicide.

Both editors are on the Harvard faculty as well as in private practice; Jacobs is academically based at McLean Hospital and Brown at Cambridge Hospital. Although a number of the contributing authors are from the Boston area, this is by no means a parochial treatise on suicide; contributors are drawn from among nationally known experts in the field.

The book is divided into four sections, sandwiched between a very brief foreword (a dialogue between Erik Erikson and Jacobs) and an afterword (two pages of reflections on suicide by Karl Menninger). Aside from historical and sentimental interest, particularly in view of Dr. Karl's recent death, little seems to be added by these two papers. Following some overview material, the first section, Foundations, contains chapters on psychological, biological, and social aspects of suicide. The second section, Understanding, begins with two chapters on suicide assessments in the general population and then has seven chapters on specific assessment considerations. The third section, Responding, has four chapters on psychodynamic and psychotherapeutic strategies and pitfalls, two chapters on treatment settings, and two chapters on the aftermath of suicide. The fourth and final section, Philosophical and Larger Perspectives, contains four chapters.

Some of the unusual contributions include the chapter by Robert Litman on assessing suicide risk in which he uses a number of dream examples from his own extensive clinical experience with patients. Alexandra Kaplan and Rona Klein view suicide in women from a relational perspective. This is an invited chapter, not part of the original symposia. I do not agree entirely with these authors that "the key to understanding the psychological experience of suicidal women is to acknowledge that, for a woman, a decision to kill herself and to therefore abandon and destroy all relatedness stands in direct opposition to the values most central to her core identity as a relational being" because I feel that there is no single key to understanding suicide, for either men or for women, and that to cite one is misleadingly simplistic. However, I found the chapter very provocative. Kaplan and Klein feel that suicidal men are more likely than suicidal women to be highly invested in an intellectualized belief in their fundamental right to kill themselves. They contrast the tendency of men to base their choices on universal principles and rules of fairness with the tendency of women to define themselves and their existence more in terms of relationships, citing a case example of a depressed man who countered his therapist's inquiry into how the patient's parents or girlfriend might feel if he killed himself by the statement, "I really don't care . . . their response has no bearing on my right to do as I please with my life." I suspect that Kaplan and Klein are looking at how people dress their rationalizations rather than the true affective state of suicidal patients of either sex.

The section on responding presents some very interesting chapters, including that of Maltzberger and Buie, who warn of the limitations of empathy in assessing suicidal patients, which contrasts with the chapter by Jacobs on using the empathic method in suicidal patients and the need to allow the patient to feel suicidal and to express that need. Maltzberger and Buie focus on seven common errors, including countertransference rage toward the patient. Zinberg has a very interesting chapter regarding the threat of suicide arising in psychotherapy that includes good case material and uses a structural model. This section concludes with a clinical interview of a suicidal patient by Leston Havens and a discussion of his interview by two experts. Another unusual chapter is Herbert Brown's on patient suicide and therapists in training.

In the section on philosophical and larger issues, a number of not very surprising stances are reached by some noted authors. For instance, Szasz emphasizes that suicide is not the responsibility of the therapist, and John Mack examines group suicidal behavior from Masada to Guyana and speculates on society's current potential for group destruction as we seem to plunge toward nuclear annihilation. Robert Lifton, writing on "Suicide: The Quest for a Future," uses Mishima's suicide as an example of his hypothesis.

Some of the material seems a little dated. John Mack's "Architectural Model" of suicide again presents the suicide of Vivienne, and Alexander Morgan's chapter, "Special Issues of Assessment and Treatment of Suicide Risk in the Elderly," extends his data analysis only to 1978 and grossly underestimates the decrease in suicide in the elderly over the past 40 years. Morgan speaks of "a small decrease" in the suicide rate among the elderly in the United States over the last 20 years and explains that this regression can be almost entirely explained by the increase that has occurred in the level of income among the elderly over this time period. That is only one of a number of possible explanations for the decrease, but the decrease in suicides among the elderly is by no means small. Overall, suicide rates have remained relatively constant in the United States for the past 50 years, but the rates for adolescents have nearly tripled. For the overall rate to remain constant there must have been a decrease in some other population, and, indeed, the decrease in the rate among the elderly is equal to the increase among adolescents. The reason it appears less dramatic is because it is spread out over a 30-year age span rather than being concentrated in a 10-year age span (e.g., 15–24-year-olds), so at first glance it appears less noticeable.

In summary, this is an excellent book that I would enthusiastically recommend to the beginner and to the expert in the study of suicide because both will find new material here. Although the suggested list price on the review copy seems a little high, I think the book is an extremely worthwhile contribution to the mental health professional's library.

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**Self-Destruction in the Promised Land: A Psychocultural Biology of American Suicide,** *by Howard I. Kushner. New Brunswick, N.J., Rutgers University Press, 1989, 268 pp., $24.95.*

The study of self-destruction is hampered by enormous conceptual and definitional problems. What is suicide? Is it a disease, an illness, a sociocultural phenomenon like marriage or divorce, a moral dilemma, or a philosophical question, as suggested by Camus? The taking of one's own life can be heroic if done in battle or to save another. In some times and places it has been considered illegal, the result of a diseased mind, or as a punishment of the gods. Self-induced death of a young person is seen as tragic, but that of an old person may be viewed as a justifiable end of suffering. The literature on suicide grows daily. Each new decade seems to involve a major conceptual reevaluation. One wishes that increased understanding would bear some proportional relationship to the volume of literature published on the subject.

Kushner's book promises a historical overview leading to a psychocultural-biological reconceptualization of suicide. This book is enjoyable to read, the style is easy and breezy, and selected chapters are excellent; however, there is a lack of integration of the various historical, cultural, and scientific components that results in an uneven and flawed work.

It is disappointing that Kushner presents his psychocultural biology as a new idea. George Engel (1) pioneered the concept of a biopsychosocial approach to illness and disease that does not differ from what Kushner is presenting except that Engel's thesis is more fully conceptualized. It is surprising that Kushner seems entirely unaware of Engel's work or even of the biopsychosocial concept, which is widely known in medicine. This apparent gap in knowledge diminishes confidence in the quality of Kushner's contribution. However, Kushner's conceptualization validates Engel's contribution.

The historical section is well written and entertaining but uneven. Kushner traces the historical attitudes toward suicide among the English settlers of New England through the rise of moral treatment and into modern times. He documents how reviled and despised suicides were by the Puritans and how moral attitudes of punishment extended to the surviving relatives. However, by concentrating on New England history Kushner neglects the rich contribution to U.S. history made by the early Spanish settlers of the Southwest. One wonders what their attitude toward suicide was and how this would alter or support his thesis.

The rise of moral treatment transformed the causation of suicide from one of moral laxity or demonic possession to that of mental disease. However, the chapter on the "Rise and Decline of Moral Treatment, 1844–1917" suffers from superficiality and neglect of the enormous number of primary sources on melancholia and suicide from the first half of the nineteenth century.

The new biological revolution suggests that altered neurochemistry, especially involving the serotonin transmitter system, may be implicated in suicide, but this work is very new and there are few and sometimes conflicting studies. Much of this work involves the study of neurotransmitters, which may be misleading. Neurotransmitters are the end result of processes occurring within the neuron. The true defect may result from altered neuronal function as a result of genetic or developmental influences, which then secondarily control the neurotransmitters. It is too early to accept uncritically as proven that altered biochemistry leads to suicide on the basis of the studies published to date, although the research results are intriguing and promising.

It is disappointing that Kushner so uncritically accepts the idea that nutritional inadequacy can lead to mass suicide, even though one of his central theses raises the question of why, when faced with seemingly similar sets of circumstances, some people commit suicide and others do not. This same question applies to group or mass suicide. People living in concentration camps were subjected to horrible conditions and severe nutritional deprivation, yet mass suicide is not a reported feature of the concentration camp experience. During World War II in Europe, when nutritional inadequacy was common, suicide rates declined (2). In the past decade, suicide rates have risen dramatically along with better nutrition in most countries in Europe. In Africa, mass starvation has been common in the last two decades, but the phenomenon of mass suicide has not been observed. To imply, as Kushner does, that the Jonestown mass suicide was a result of nutritional deprivation of tryptophan or other serotonin precursors is at best a hypothesis and at worst a rank speculation. Further, to imply that the sixteenth-century English settlers of Jamestown were apathetic because of a similar dietary deficiency is unsupported speculation.

In summary, this is a book worth reading critically. It will stimulate ideas and induce frustration because of overgeneralizations and the frequent uncritical acceptance of underdeveloped hypotheses. Kushner is often dogmatic when a more flexible concept would be appropriate. His book is interesting and provocative, but it also highlights the folly of trying to bring together findings in several independent fields of research without first developing an articulated model of how the component fields interact.

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## GERIATRIC PSYCHIATRY

**Geriatric Psychiatry,** *edited by Ewald W. Busse, M.D., and Dan G. Blazer, M.D., Ph.D. Washington, D.C., American Psychiatric Press, 1989, 695 pp., $55.00.*

Geriatric psychiatry has come of age in the United States. The recent decision by the American Board of Psychiatry and Neurology and the American Board of Medical Specialties to denote "added qualification" for geriatric psychiatry culminates the slow but steady process of recognition that this field is sufficiently unique to require special demarcation. Supported by the Council on Aging of APA, the Committee on Aging of the Group for the Advancement of Psychiatry, the Center on Aging (now the Mental Disorders of the Aging Research Branch) of the National Institute of Mental Health, and, more recently, the American Association of Geriatric Psychiatry, the professional identity of geriatric psychiatry has emerged at a time when the elderly are the fastest growing portion of our population. Indeed, the demographic imperative has proven most powerful, and despite governmental policies that attempted to limit the resources spent for the mental health needs of the elderly, this subspecialty has begun to emerge in a more nearly completed form. (One might be tempted to interpret previous Medicare reimbursement regulations as an outright attempt to stifle the development of the field.)

In this evolutionary context, the publication of *Geriatric Psychiatry* is most welcome. Anyone who looks at the book will immediately recognize that this is largely the product of professionals working or trained at Duke University; thus, it reflects a long tradition of involvement in geriatrics and gerontology. It is not a reissue of the authors' handbook (1) but an entirely new text that expands its focus and presents a balanced, comprehensive, and current view of the field, impressively conveying the breadth and depth of available knowledge.

Busse and Blazer have constructed their volume in four basic sections. (There is a brief closing section that is, in great measure, philosophical and historical as well as future looking.) The sections pay attention to the basic science of geriatric psychiatry (including cultural, neurobiological, physiological, psychological, socioeconomic, and epidemiologic perspectives), the diagnostic workup, a review of psychiatric disorders, and consideration of treatment approaches.

One of the most evident strengths of this text is its clear roots in geriatric medicine and gerontology, and this is manifest throughout each of the sections and the individual chapters. I particularly appreciate those chapters which enlarge my view and draw my attention to the broader perspectives that must be considered in geriatric practice. The opening chapter by Busse, Rowe's discussion of the physiological changes that occur with aging, George's consideration of social and economic factors, and Sullivan's review of diet, nutrition, and exercise all contribute to enhancing an understanding of the discipline's overall context. An epidemiologic theme is interwoven throughout the section on clinical disorders, reflecting the tradition of the Duke program and Dr. Blazer's particular interests, and this provides a valuable backdrop for the descriptions of psychiatric disturbances. Clearly, the authors of these chapters are very experienced clinicians as well as researchers, and they go to great lengths to clarify the unique or special problems presented by geriatric patients. The editors must have placed emphasis on the need to balance research findings with practical clinical information. They are successful. Moreover, the chapter authors often convey the limitations of available research, and I was pleased to see no grandiose efforts to present the field as fully formed or completely understood. This is well exemplified in the chapter on anxiety disorders by Brickman and Eisdorfer and in Blazer's chapter on affective disorders.

The chapters on treatment are straightforward, useful summaries with carefully considered recommendations for therapy. In addition to the chapter by Sullivan already noted, there are useful discussions on pharmacotherapy, psychotherapy, the treatment of the elderly in inpatient and long-term care settings, and a description of the development of community-oriented care. The latter is presented from a health services delivery perspective and provides an important counterpoint that emphasizes the need for a broader view by the practicing clinician.

Some quibbles. I looked for a clear-cut discussion about the differences in patient populations encountered in inpatient settings (both psychiatric and consultation-liaison), long-term care, ambulatory settings, and home-care settings. Although much of the psychopathology encountered in each of these sites is alike, distinctive differences do exist and need to be considered systematically. The treating clinician would benefit from such a review. Although components of the necessary material are scattered throughout the book, a concise comparative discussion would prove helpful. My second quibble involves the presentation format in the text. In the clinically oriented sections, brief summary tables that concisely review principles for treatment and therapeutic interventions would assist the reader who seeks a quick review of a specific question. Beyond these, I have little to criticize.

*Geriatric Psychiatry* certainly deserves a place on the bookshelf of anyone aspiring to develop skills in this specialty as well as the general psychiatrist who wants to deepen his or her understanding of unique aspects of the field. It is a core text. Beside it I would place *Geriatric Neuropsychology* by Marilyn Albert and Mark Moss (2) and *Clinical Neurology of Aging* by Martin Albert (3). These three together form the basis of a very usable reference library that will introduce the clinician to this exciting, useful, and rapidly growing field.

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**Dementia Care: Patient, Family, and Community,** *edited by Nancy L. Mace. Baltimore, Johns Hopkins University Press, 1989, 392 pp., $34.50.*

This didactic work provides many compassionate management strategies and very candid analyses of research studies for patients as well as for primary and secondary caregivers. The contributing authors represent diverse disciplines, and their experiences range from hands-on in hospitals and nursing homes to academia, consultantships, and private practice. Each author offers the unique insights culled from clinical management, research, and involvement with dementia patients and their families on many levels. What emerges is a volume confirming that the functioning of the patient can be maximized with appropriate care and intervention.

The convergence of neurology and psychiatry is underscored. Assessment is advocated as an ongoing process involving not only the reciprocal interactions among patient, family, and community but the patient's immediate physical and psychosocial environment.

Part one, The Patient, consists of seven chapters that in simple, straightforward language differentiate among medical diagnosis, psychosocial assessment, and differential diagnosis for the nonmedical reader, concluding that these are not independent processes. This section does much to bolster the understanding of the caregivers and the dignity of the patient. Practical insight into the meaning of behavior is offered—for example, "A patient who poses a problem because of inappropriate sexual remarks to the staff may really be trying to restore a self-concept of physical attractiveness in the past." Truisms regarding aging, such as that personality traits become more ingrained, are mentioned, but, equally important, the various authors stress building on the patient's resources and support systems.

Practical questions such as, How does the family react emotionally to problems? How does the family cope? and How does the family solve problems? are raised. The authors also raise sensitive issues: Who should become a caregiver? How should the diagnosis of Alzheimer's disease be presented to the patient and the family? Is drug use and misuse causing or contributing to delirium and dementia? Who should conduct assessments with the patient and the family?

Descriptions of behavioral interventions that maximize functioning and health maintenance are packed into every chapter. The pros and cons of interventions that attempt to change the patient are raised consistently. Ethical issues are inculcated in principles of care, and the authors clearly are patient advocates: "The use of agents for their nonspecific, sedative effects to produce a more cooperative patient is to be avoided." Many areas requiring further research, such as the use of behavior modification and supportive milieu therapy and the patient's level of perception, comprehension, and attention, are suggested.

The family is the focus of the four chapters in section two. The opening pages are dotted with the experiences of primary caregivers, which sets the stage for the exploration of common themes in family encounters, demographics of caregivers, assumptions surrounding caregiving, and the physical, psychosocial, financial, and legal issues that arise. The chapter entitled "Design of the Home Environment for the Cognitively Impaired Person" emphasizes that the normal sensory changes associated with aging create the need for special environments. Making the home environment safe is not confined to matters of architecture and security, although these issues are addressed. Rather, the goal is to use environmental design to support and enhance the patient's attention span, life style, and social interchange.

Just what constitutes respite care is dovetailed with issues of cost containment and minority programming. However, respite care is in short supply and has many limitations. The author of this chapter states with conviction that "all situations will not be served by respite care." The barriers to respite care presented in this chapter need further study. The results of delay, denial, and ineptitude in addressing legal and financial considerations are summed up in one word—impoverishment. The key issues that caregivers need to consider—guardianship, power of attorney, living wills, probate, joint tenancy trusts, and financial entitlements—are discussed in depth. This chapter is required reading for caregivers.

Part three has as its central focus the community, including approaches to long-term settings, use of volunteers, and public policy. The book concludes with a chapter entitled "Changing Public Policy for Dementia Care." It challenges the reader to action; decision makers respond to advocates who are voters.

This book should emerge as a solid reference for caregivers, medical personnel, and allied human service professionals. Researchers, too, are offered a wealth of ideas for further investigation. Information regarding complex issues is conveyed with pithy explanations, congruent tables, concise chapter summaries, and references.

Perhaps the outstanding contribution of this book is that although numerous studies are cited, the scientific data do not overpower the human message. Attention to the patient's comfort level and to the development of nonjudgmental attitudes toward caregivers pervades the volume. *Dementia Care* is recommended reading for all who would like new insights and a hopeful message regarding innovative possibilities in the care of the patient with dementia.

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**Society, Stress, and Disease, vol. 5: Old Age,** *edited by Lennart Levi, M.D. New York, Oxford University Press, 1987, 377 pp., $175.00.*

This is an old book about old age. Although the date of the WHO-sponsored symposium on which this volume is based is conspicuously absent, it would not take a Baker Street Irregular to observe the curious facts that three of the contributors are listed as deceased, several funding agencies are thanked for their generosity in the early 1970s, and the future tense is used in a reference to 1976. In the preface, dated June 1987, Dr. Levi lists under the heading New Trends a number of WHO recommendations to which the editor hopes this series of symposia and books may have contributed "to some modest degree." This is a demure aspiration and begs the question of what the book might offer an interested gerontologist considering its purchase in 1990.

The answer is mixed. The best chapters review different psychological theories on aging; the differential response to old age in countries such as Sweden, India, France, and Kenya; how to prepare people for retirement; and how the social policy of the Soviet Union safeguards the health and well-being of its elderly. Many of the chapters have delightful (and hopeful) quotations about aging, and one, by Corson and Corson, chronicles the late-life achievements of a number of individuals still active in their 80s and 90s. There is a considerable amount of descriptive data that generally support the "use it or lose it" school, and, overall, the psychosocial perspective outpoints the biological by a large margin.

The bad news is that the book contributes to the transformation of the term "holistic" into an uncomplimentary adjective. Boxes, arrows, and Venn diagrams link such things as death and disengagement to decrease of resources and loss of control to low sex and maternal drives, the "playing dead reaction," and increased pepsin levels. Another chapter, contrasting harmonious aging ("eugeria") and disharmonious aging ("dysgeria"), lists healthy skin color, a normal genital tract, and a preponderance of alpha waves and nonextremist religious, political, and racial views in individuals with eugeria as opposed to wrinkles, vaginal prolapse, and relatively more slow-wave activity and critically intolerant behaviors in those afflicted with dysgeria.

In part the problem is editorial. Specific chapters, such as those advocating pet-facilitated therapy and nonverbal communication therapy for the aged, are juxtaposed with overarching reviews of the "problems, challenges, and future trends" in geriatric care in Western countries. This alternating microscopic and macroscopic look at old age produces a somewhat unfocused final view, reflected in Aubrey Kagan's unenviable task, a chapter entitled "Synopsis of General Discussion." Ever the statesman, Kagan chooses simply to quote the contributors piecemeal but at length. It is hard to be too critical of this, given the focal range of contributions on dogs, cats, pensions, bowel function, and death.

At age 42, I felt that the worth of this book on aging was established in one of Alastair Heron's chapters, "The Concept of Functional Age," in which he punctures the rather disagreeable notion of "too old at 40." It would have been more reassuring to me, however, had the argument been based on something stronger than individual differences.

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## TEXTBOOKS

**Psychiatric Interviewing: The Art of Understanding,** *by Shawn C. Shea, M.D. Philadelphia, W.B. Saunders (Harcourt Brace Jovanovich), 1988, 554 pp., $25.00.*

Writing a book to teach or improve a skill is a formidable challenge. The constraints of the written format often entrap both author and reader in lethal tar pits of viscous description, disorienting direction, and daunting detail. Whether it is a pamphlet designed to teach the teenager the mechanics of operating an automobile or a book endeavoring to teach competitive swimming strokes, most of these efforts fall far short of "live" instruction, supervision, or coaching. The skills necessary for psychiatric interviewing are numerous and variable. At least two individuals with unique experience, temperament, and outlook engage in an almost infinite complexity of exchanges and interactions that are affected by countless endogenous and exogenous variables—including the willingness and capacities of each party to participate, perceive, comprehend, and communicate. It is no wonder that, despite the fundamental importance of psychiatric interviewing for clinical assessment, diagnosis, and treatment, relatively few books are specifically devoted to the subject. Further, most among this small number of books go unnoticed. The one or two valuable exceptions (1, 2) have avoided the dialogue format ("the patient says . . . ; the psychiatrist responds") that requires a dramatic writer of Shakespearean prowess to sustain a reader's interest beyond a page or two.

Shawn Shea enters this treacherous arena and dares to amplify the challenge by declaring the ambitious goal of crafting a book on psychiatric interviewing that is not only a "practical guide for psychiatrists, psychologists, counselors, social workers, nurses, and other mental health professionals" but also a "current textbook for medical students and nursing students as they study psychiatry." The director of a course on psychiatric interviewing at the Western Psychiatric Institute and Clinic in Pittsburgh, Dr. Shea states in his preface, "I felt a practical textbook, emphasizing the integration of engagement, diagnosis, and treatment planning, would be very helpful. To my surprise, I could not find such a book." As I have said, other psychiatrists, including MacKinnon and Michels (1) and MacKinnon and myself (2), have struggled to write such books, which have met with a considerable degree of success based on published reviews and reader acceptance (the former has sold over 80,000 copies and continues to sell several thousand texts per year). This unintended slight, combined with Dr. Shea's ambitious goals, cast a gauntlet of skepticism in my direction. However, in a fashion that parallels a skillfully executed psychiatric interview, Dr. Shea engaged and disarmed me with a book that blends a scholarly mastery of the subject with taut organization, skillful writing, and charm. *Psychiatric Interviewing: The Art of Understanding* differs sufficiently from and adds substantially to previous texts on this subject to make a unique and substantive educational contribution for students and practitioners of all the mental health disciplines.

The writing style of the book is highly personal. The first person plural is used throughout the text—a technique that successfully establishes an intimate tone, not unlike what occurs in dyadic supervision. The form also provides a rhetorical flexibility that allows the author to combine, successfully, many didactic forms such as referenced data, personal opinions, anecdotes, case examples, exhortations, and admonitions. Suffused with charm, humor, and intrigue, Dr. Shea's oratorical style proves to be an ingenious educational vehicle with which to convey important points about the technique and process of the psychiatric interview. The result is that the reader's interest and imagination are sustained throughout the book. In fact, this book can be read with interest and enthusiasm from cover to cover, almost like a novel.

*Psychiatric Interviewing: The Art of Understanding* is divided into three parts. Part one, The Fundamentals of Interviewing, concerns itself with the basic principles of the skill. Of necessity, this section reviews fundamental definitions, guidelines, and issues that are essential for the novice. Dr. Shea also unflinchingly takes on difficult and often overlooked subjects such as "clinician genuineness" and skillfully dissects, defines, and explains the implications of the issue. This section is enhanced by examples of the advantages and disadvantages of a variety of techniques, including using open-ended versus closed-ended questions, probing versus nonprobing techniques, fact finding versus opinion finding, and structured versus nonstructured interviewing. The examples used are interesting, clear, and believable and will complement "live" supervision. The focus is on the dynamic process of the psychiatric interview, which Dr. Shea correctly understands is a highly structured discipline with the potential to be a breathtaking artistic expression.

The chapter entitled "Nonverbal Behavior: The Interview in Mind" is especially stimulating and useful. In this consideration, Dr. Shea isolates the basic principles of nonverbal behavior, including proxemics (the manner in which people are affected by the distances between themselves and objects in the environment), kinetics (the study of the body in movement), and paralanguage (how messages are delivered, including such elements as the tone of voice, loudness of voice, pitch of voice, and fluency of speech). Characteristically, Dr. Shea delves into such sticky questions as when it is and when it is not appropriate to touch a patient.

The last chapter in part one deals with the organization of data from the interview and the development of a treatment plan. Dr. Shea does an excellent job of introducing the reader to the use of *DSM-III-R;* however, the didactic quality plummets as the author introduces his own systems analysis paradigm for organizing and understanding data derived from clinical assessments. The basic problems with Dr. Shea's paradigm are that it is largely self-evident, it is somewhat idiosyncratic, and it does not provide sufficient guidelines, organization, and structure for the student or the practitioner to develop and write up a cohesive case formation and treatment plan. I view this to be an important deficiency of the book because students and educators must look elsewhere to have case formulation and treatment planning presented in a more structured and applicable format.

Part two focuses on interviewing techniques for patients with mood disorders, psychoses, and/or personality disorders. The author enriches these sections with a wealth of data about the respective symptoms and syndromes. The text is suffused with illustrative and captivating clinical examples. The result is that, in addition to learning a great deal about interviewing techniques, the reader also gains multidimensional knowledge of several major psychiatric disorders. The disadvantage of this approach, however, is that the author occasionally loses his way and transforms the book into a general textbook of psychiatry. For example, tables on common causes of delirium and organic causes of psychoses are included. The overall result is a capricious selection of several subjects that are expanded beyond the central theme of the psychiatric interview and other important entities are omitted.

Part three deals with advanced techniques of interviewing. An important and successful chapter focuses on exploring suicidal and homicidal ideation and potential. Dr. Shea does an excellent job of portraying skillful use of the psychiatric interview to assess (and diminish) suicidal risk. Unfortunately, he devotes only two pages to the use of the psychiatric interview to explore homicidal ideation and risk—an area that is of extraordinary importance to both the student and the advanced practitioner. He states, "The approach to homicidal ideation is a great deal foggier than the approach to suicidal ideation. The reason for this problem is the fact that risk factors for homicide are not as well delineated. In fact, to my knowledge, no study has indicated an effective way of accurately predicting homicide" (p. 437). In actuality, there is a large, solid, and applicable body of knowledge related to the assessment and reduction of aggressive risk, and these data relate importantly to multifarious aspects of the psychiatric interview. Noticeably missing from the bibliography at the end of the chapter are seminal papers in this area by such authors as Tardiff, Dietz, Lion, Eichelman, Monroe, Bell, Silver, and many others. The appropriate use of the psychiatric interview to assess and diminish violent risk is a critical skill for every practitioner, and its virtual omission in this text represents a missed opportunity.

The last two chapters of the book, "Vantage Points: Bridges to Psychotherapy" and "The Art of Moving With Resistance," are creative high points of the book. In the former chapter Dr. Shea addresses often overlooked areas, such as intuitive responses on the part of the interviewer, the role and use of the clinician's own fantasies, and issues related to self-disclosure. The concluding chapter of the book approaches patient resistance from many perspectives. The novice interviewer is taught to recognize resistance in its many forms and is instructed in useful techniques and approaches to convert resistance into opportunities for insight and advancing the goals of treatment. In summary, I highly recommend *Psychiatric Interviewing: The Art of Understanding* for both students and experienced practitioners of the full range of mental health disciplines. Rich in information, wisdom, humor, and charm, this book teaches not only interviewing skills but also the attitudes and behaviors that underpin the therapeutic personality and process.

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**Outpatient Psychiatry: Diagnosis and Treatment, 2nd ed.,** *edited by Aaron Lazare. Baltimore, Williams & Wilkins Co., 1989, 726 pp., $75.95.*

In this second edition of *Outpatient Psychiatry,* Aaron Lazare has put together a crisply edited textbook that beautifully embodies the modern principles and perspectives which define our evolving discipline. The work contains 50 chapters organized into five sections: Conceptual Approaches for Clinical Practice, Data for Assessment, Differential Diagnosis of Psychiatric Presentations With Known Organic Causes, Selected Problems in Outpatient Practice, and Aspects of Treatment in

Outpatient Practice. Notably, Lazare wrote or co-wrote almost one-third of the chapters, and all but seven come from contributors at his own department at the University of Massachusetts or those from Harvard affiliates. This concentration of authorship along with the concise format and lucid writing style allows the book to speak with a clear voice. Unlike some other edited texts, it is easy to read, cohesive, and nonrepetitious.

The first section is the strongest. In simple but elegant fashion, Lazare advances a model of psychiatric practice firmly grounded on multidimensional thinking and rigorous testing of the clinical data. This may be second nature to experienced clinicians, but to see this model articulated in an introductory textbook is refreshing. The need to approach clinical problems in a flexible manner, using multiple orientations and then searching for the best fit between theory and clinical reality, is emphasized throughout the book. To accomplish this, the biological, psychological, sociocultural, and behavioral perspectives are each reviewed in separate chapters. Sherman Eisenthal's comprehensive account of sociocultural psychiatry is particularly outstanding. This even-handed review of psychiatry's major paradigms is followed by a chapter on hypothesis testing. Lazare describes how to organize clinical data into a series of assertions capable of being weighed and challenged. Given the central importance of this task, this chapter would have benefited from elaboration and examples. The last chapters in this first section codify Lazare's earlier work on the "customer" aspects of patienthood and help seeking and describe an interesting model of psychotherapy as negotiation.

The creativity and vitality of these introductory chapters is less apparent in the following sections. Here we are presented with the more standard renditions of the mental status examination, lists of medical illnesses that cause psychiatric symptoms, and a sampling of diagnostic categories described in "*DSM-III-R*-ese." Among the latter, Rogoff's chapter on the mentally retarded mentally ill is quite good, and Krystal et al. provide an illuminating review of anxiety disorders. In contrast, some of the information on schizophrenia is antiquated and, at times, misleading.

The last section contains five chapters on individual, group, family, behavior, and rehabilitative therapies. In the discussion of individual therapies, Docherty provides a masterful, concise review of the literature on process and outcome variables in psychotherapy research and follows with a description of currently established treatment modalities. Moss and Lieberman provide a thorough explication of behavior therapy with a step-by-step demonstration of its strategies. The inclusion of a chapter on the psychology of psychopharmacology is a welcome addition.

This book is like a dinner which begins with such a splendid appetizer that the rest of the meal, good though it may be, suffers by comparison. Lazare's introductory section is bubbling with fresh ideas and vitality. However, rather than developing and exemplifying the multidimensional, hypothesis-testing model of patient care, the book reverts to the all-too-standard descriptions of disorders and treatments that can be found in other comprehensive works. In addition, issues specifically pertinent to the outpatient setting, such as payment, reimbursement, and collaboration with other health professionals, are not included. The failure to address these topics, along with the fact that the lion's share of this work reiterates information found in general textbooks of psychiatry, forces the question of whether this book truly documents a knowledge base specific to the outpatient setting. Elaboration of the proposed treatment model, along with the addition of topics more germane to ambulatory practice, would convert this book from a good one to a great one. As it is, *Outpatient Psychiatry* provides a strong introductory text for medical students and psychiatric residents.

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*Reprints of Book Forum reviews are not available.*

# *Letters to the Editor*

## Fluoxetine-Induced Elevation and Prolongation of Tricyclic Levels in Overdose

SIR: Since Vaughan's description in 1988 of a fluoxetine-tricyclic interaction (1), a series of reports, many in this journal, have warned of elevated plasma levels of tricyclic antidepressants when fluoxetine is used concurrently. We now report a suicide attempt by a woman who ingested imipramine while taking fluoxetine daily. This case highlights two important aspects of tricyclic overdose in patients receiving fluoxetine: extraordinarily high levels of the tricyclic and prolonged elimination of the tricyclic.

> Ms. A, a 61-year-old woman with a long history of depression, was admitted to the hospital after she attempted suicide by ingesting "a handful" of imipramine tablets. Six months before admission her long-standing imipramine regimen had been changed to fluoxetine, 20 mg/day, because of a recurrence of her depression. She did well and continued to take this dose of fluoxetine several months without incident.
>
> After ingesting the imipramine, Ms. A became unconscious and required intubation and mechanical ventilation. Her imipramine level on admission (approximately 2 hours after ingestion) was 1980 ng/ml and her desipramine level was 126 ng/ml. Four days later, her imipramine and desipramine levels were 868 and 152 ng/ml, respectively. One week after the overdose, her imipramine and desipramine levels were 306 and 122 ng/ml, respectively. She had a sinus tachycardia during her first 48 hours in the hospital, and ECG changes (maximum QRS interval=0.10 seconds; corrected maximum Q-T interval=0.52 seconds) were mild and normalized before discharge. Except for an aspiration pneumonia that resolved when she was given antibiotics, she had an uneventful recovery.

Previous reports of tricyclic overdoses (2, 3) defined a major overdose as one that resulted in a maximum total plasma level of more than 1000 ng/ml, typically in the range of 1000–2000 ng/ml. This patient's peak combined imipramine/desipramine level of 2106 ng/ml was among the highest levels reported. Since fluoxetine can raise desipramine levels two- or threefold (4), the potential for achieving very high tricyclic levels in overdose is increased. As a suicide gesture, some patients may ingest what they think is a "safe" amount of a tricyclic antidepressant while taking fluoxetine, which could have fatal consequences. We believe that physicians who prescribe fluoxetine and patients who take it should be aware of this drug interaction.

A second issue is the effect of fluoxetine on the elimination phase of the tricyclic. Spiker et al. (5) reported prolonged toxic levels of tricyclics after overdose in some patients. Ms. A's combined tricyclic level of 1020 ng/ml 96 hours after overdose indicates a particularly long elimination phase. Typically, acute management of a serious tricyclic overdose has involved cardiac monitoring for 24–48 hours or until plasma levels fall below 1000 ng/ml. As this case illustrates, for patients taking fluoxetine, tricyclic levels may remain elevated for a prolonged period following overdose, thus complicating the clinical management of the overdose. Given the increasingly widespread use of fluoxetine for the treatment of depression, awareness of fluoxetine-induced elevation and prolongation of tricyclic levels in overdose is an important clinical issue.

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## Fluoxetine Treatment of Depression in Patients With HIV Infection

SIR: Judith G. Rabkin, Ph.D., M.P.H., and Wilma M. Harrison, M.D. (1) reported on the efficacy and side effects of imipramine for the treatment of major depression in individuals with HIV infection. Eight of nine patients responded in an open 12-week trial. The authors mentioned that one patient was effectively treated with fluoxetine after showing no response to imipramine. We report here similar improvement in major depression in two patients with HIV infection treated with fluoxetine.

> Mr. A, a 45-year-old man with a 1-year history of AIDS, had been given a diagnosis of pneumocystis pneumonia and had been treated with zidovudine since the diagnosis was made. He presented with a 3-month history of symptoms meeting the *DSM-III-R* criteria for a major depressive episode, including pervasive depressed mood, anhedonia, feelings of worthlessness, insomnia, anorexia, weight loss, suicidal ideation, marked decline in energy level, and impaired concentration. There was no evidence of cognitive impairment according to the Mini-Mental State examination. Fluoxetine, 20 mg each morning, was begun. By week 4 of treatment, Mr. A was euthymic and reported complete remission of all depressive symptoms,

with the exception of low energy, which had improved but still continued at the level he had experienced before the onset of the major depression. Fluoxetine was well tolerated; the only complaint was an initial experience of "feeling wired" that improved by week 4 of treatment.

Mr. B, a 28-year-old man with HIV infection, experienced unexplained low-grade fevers, night sweats, low energy, and weight loss. He had a 2-month history of pervasive depressed mood, anhedonia, suicidal ideation, insomnia, anorexia and worsening of weight loss, lower energy level, and impaired concentration, meeting the *DSM-III-R* criteria for a major depressive episode. The Mini-Mental State examination did not reveal cognitive impairment. Treatment with fluoxetine, 20 mg each morning, was initiated, and the dose was increased to 40 mg after 4 weeks of treatment because of lack of response. By week 6 of treatment, Mr. B reported improvement in mood and sleep, increased interest and ability to experience pleasure, and remission of suicidal ideation. By week 8 of treatment, the patient stated that he felt he was back to baseline, with euthymic mood, improvement in energy level, and remission of other symptoms. At this time zidovudine was begun. The patient reported weight gain and further improvement in energy level, as well as remission of fevers and night sweats. Fluoxetine was continued and was tolerated extremely well; Mr. B denied any side effects.

These case reports support the findings of Drs. Rabkin and Harrison that major depression in patients with HIV infection is responsive to antidepressants. Other investigators have reported similar findings in an open trial of fluoxetine in such patients (2). Fluoxetine was well tolerated by our patients, despite their medical illness. Both of them reported improvement in appetite, and neither reported weight loss, a potential side effect of fluoxetine. Recent reports of the sensitivity of patients with HIV infection, especially those with AIDS, to anticholinergic drugs suggest that fluoxetine may be better tolerated in this medically ill population (3). However, we recommend that fluoxetine be used with caution in patients with impaired liver function or other medical problems that could increase the risk of side effects from the drug.

There is recent evidence that major depressive symptoms in some patients with HIV infection may represent a secondary depression, resulting from the effects of HIV on the CNS, and may respond to treatment with zidovudine (4), as has been reported for zidovudine-responsive neuropsychological impairment in individuals with HIV infection (5). We conclude that a trial of antidepressant medication should be considered for patients with HIV infection who show evidence of major depression. Controlled study will be necessary to determine whether specific treatments are necessary for primary major depression, as compared to secondary depression, in these patients.

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## Anticonvulsants Combined With Nifedipine for Epilepsy in Adults

SIR: The regulation of neural transmission, the presynaptic release of neurotransmitters, and the etiology of epilepsy are all influenced by calcium ions. A reduced extracellular level of calcium ions increases the excitability of neurons. The flow of calcium ions regulates the proximal depolarization shift in neurons (1). Lowered flow of calcium ions to the presynaptic site of neurons induces the anticonvulsive effect of phenytoin (2). Due to the crucial role played by calcium ions in the regulation of neuronal excitability, central-acting calcium antagonists might be considered as potential anticonvulsants. Nifedipine, which crosses the blood-brain barrier, proved to be anticonvulsive in animals (3, 4); therefore, it could reduce the incidence of seizures in patients with intractable epilepsy. Eighteen ambulatory patients (six female and 12 male, aged 18–49 years) took part in a double-blind controlled study, which was approved by the local ethics commission. Six had been suffering from partial seizures (four simple, three sensory, one motor, and two complex) and 12 from partial seizures (eight simple, six sensory, two psychic, and four complex) with secondary generalization for 3–34 years. Eight patients were taking carbamazepine, seven were taking carbamazepine and valproic acid or phenytoin, and three were taking the combination of carbamazepine, phenytoin, and valproic acid or phenobarbital. Serum levels of all anticonvulsants given were measured monthly. Additional treatment with nifedipine, 60 mg/day, was started, and serum levels of all anticonvulsants given were measured on days 2, 3, 7, and 10 and monthly thereafter.

No influence of the additional calcium antagonist therapy on blood levels of the anticonvulsants appeared. Seizures were counted for 4 months before and after the additional treatment with nifedipine. Anticonvulsive therapy with nifedipine resulted in a statistically significant ($p<0.005$, Student's t test) reduction in the incidence of seizures in 15 patients. Three subjects discontinued nifedipine therapy because of slight headache, dizziness, and nausea. An absence of seizures occurred in four patients for 1 month and in one subject for 3 months.

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## Catatonia Unexpectedly Reversed by Midazolam

SIR: Midazolam is an ultra-short-acting parenteral benzodiazepine used to produce sedation before surgery or diagnostic procedures. I wish to report on a case of catatonia that was serendipitously reversed by this agent.

> Ms. A, a 24-year-old patient with catatonic schizophrenia who had had one previous admission, decompensated when she stopped her maintenance medication (loxapine, lithium, and amantadine) and was hospitalized with hallucinations, paranoia, motor retardation, and withdrawal. Despite reinstitution of her medications, her immobility worsened and she became mute. She remained alert but could not eat or drink, necessitating placement of a nasogastric tube. Lorazepam, 1 mg q.i.d. given by tube, was added, but it failed to produce an appreciable response after 3 days. When the nasogastric aspirate tested hemepositive, a gastroenterologic consultation was sought, and it was recommended that the tube be removed and an endoscopic examination be done. Prior to the procedure Ms. A received midazolam, 5 mg i.m. followed by 5 mg i.v., shortly after which she began conversing loquaciously in an appropriate though tangential and delusional vein. She moved easily and cooperated for the endoscopy (the results of which were negative), after which her immobility and mutism returned.
>
> Since Ms. A was still unable to take medication by mouth, it was decided to give midazolam, 5 mg i.m. Again, she briefly emerged from her catatonia, only to relapse after 15 minutes. The next day midazolam, 10 mg i.m., produced more impressive and sustained motor and verbal improvement, although thought disorder and delusions remained. After each injection the patient's blood pressure rose inexplicably to 180/120 mm Hg, so further injections were withheld, but by now she could take lorazepam, 2 mg q.i.d., and loxapine, 25 mg b.i.d., by mouth. Her catatonia improved, but her psychotic symptoms did not. A week later she began refusing all medication, suffered a partial catatonic relapse and worsening of psychosis, and went on to a prolonged course of illness.

Reports of reversal of catatonia by parenteral lorazepam (1), diazepam (2), clonazepam (3), and lormetazepam (4) share similarities with the case of Ms. A, notably that catatonic symptoms were selectively improved and improvement was sustained after changing to an oral benzodiazepine (and sometimes adding an antipsychotic). The initial failure of oral lorazepam suggests that high or rapidly rising serum levels might be necessary to break a "catatonic threshold."

The blood pressure elevations were unexpected and not readily explainable pharmacologically. Intravenous midazolam has been associated with respiratory depression and should be used only when resuscitation equipment is present. Given the hazards, one of the other parenteral benzodiazepines might be a better first choice in most circumstances.

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## Effects of Administering Antidepressants to Patients Receiving ECT

SIR: The recent report of the APA Task Force on ECT (1) has renewed clinical and investigative interest in the proper use of ECT for patients with severe affective disorders. The side effects of ECT are well-known; they include transient memory loss, muscle aches, headaches, systemic hypertension during seizure, tachycardia, and occasionally premature ventricular contractions (2). The mortality risk has been estimated at 1/10,000 patients (2). Consensus is lacking about the safety and efficacy of administering psychotropic medications while patients are receiving ECT. El-Mallakh (3) reported that receiving lithium during ECT increases a patient's risk of developing neurotoxicity. However, many clinicians give neuroleptics, benzodiazepines, and antidepressants during ECT. Little is known about the risks or benefits of such practices.

In order to examine whether the concurrent administration of antidepressants increases the risk of acute delirium during ECT, influences the length of patients' hospital stay, and alters the risk of relapse (as measured by readmission rates), we retrospectively examined two groups of inpatients at a university hospital who met the *DSM-III-R* criteria for major depression. One group included elderly patients ($N=73$; mean±SD age=68.1±7.8 years; mean±SD number of concurrent medical diagnoses=2.5±1.9) and the other, young adult patients ($N=38$; mean age=29.2±5.5; mean number of concurrent medical diagnoses=0.8±1.2). Of the 73 older patients, 17 received ECT, nine of whom received concurrent antidepressant medication. Of the 38 young adult patients, three received ECT, two of whom received concurrent antidepressant medication. Only one geriatric patient experienced delirium that exceeded the expected mild post-ECT confusional state. The patient received amoxapine, and the delirium was of such severity that ECT was discontinued.

Other findings showed that for both the elderly and the young adult patients receiving ECT, hospital stays were longer than for the patients receiving medication only (elderly patients: 46.2±25.2 days and 22.9±11.0 days, respectively; $t=8.82$, $df=71$, $p<0.001$; young adult patients: 31.5±14.8 days and 12.3±6.0 days; $t=6.26$, $df=36$, $p<0.001$). The older patients who received ECT and concurrent antidepressants did not have longer hospital stays than those who received ECT alone (46.1±32.3 days and 46.3±13.2 days, respectively). As only three young adult patients received ECT, similar comparisons were not made for the young adult group.

Fifty-one geriatric patients (10 ECT patients and 41 medication patients) were reliably followed for 24 months. Of the four patients who received ECT and antidepressant medication, three relapsed within 24 months. Of the six patients who received ECT alone, two relapsed. Of the 41 patients who received medication alone, 15 (36.6%) relapsed within 24 months. Similar comparisons for the young adult patients were not made because of their chaotic follow-up patterns and scant numbers.

Results from this small retrospective study suggest the following conclusions. 1) Giving antidepressant medication to elderly patients receiving ECT does not increase the risk of delirium or prolong hospitalization. 2) Hospital stays were longer for geriatric and young adult patients who received ECT than for patients receiving medication alone. We believe this represents a severity of illness factor (ECT patients were sicker) and does not suggest that ECT caused prolongation of hospitalization. 3) Readmission rates (our measure of relapse) for all geriatric patients was high, regardless of treatment, and approximated the 53.8% 1-year relapse rate found by Georgotas et al. for geriatric patients receiving nortriptyline as maintenance medication (4). Future investigations should examine more refined physiologic measures of ECT, such as total seizure time, and correlate physiologic measures with outcomes such as length of hospital stay, relapse rate, and risk of delirium.

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## Use of Maintenance ECT for Elderly Depressed Patients

SIR: Commenting on the review by Robert F. Prien, Ph.D., and Alan J. Gelenberg, M.D. (1) of preventive treatment of bipolar disorder, Charles Kellner, M.D., and associates (2) raised the issue of maintenance ECT. In our department seven patients have now been treated with maintenance ECT for nearly 3 years (mean±SD=34.0±1.9 months, range=28–44 months).

Among these elderly patients (mean±SD age=75.0±3.5 years, range=56–86 years) responding poorly to mood stabilizers—in particular, lithium and carbamazepine—one suffers from bipolar disorder according to the *DSM-III-R* criteria, five from recurrent major depression, and one from schizoaffective disorder; their first episodes occurred between 7 and 52 years ago (mean±SD=31.2±5.9). Before inclusion in the maintenance program, a positive response had been obtained with a curative series of six to 10 ECTs (mean±SD=8.0±0.4).

The mean±SD total number of maintenance ECTs in the group is presently 25.8±2.4 (range=19–36), and four patients are continuing in the program. Maintenance treatment was delivered every 3–5 weeks for the first 4 months and every 4–8 weeks from the 12th month onward. The mean±SD scores on the Hamilton Rating Scale for Depression (31.4±1.7 [absence of symptoms=1]) and the Brief Psychiatric Rating Scale (29.5±2.2) remained low and stable during the maintenance period. Whereas patients had spent a mean±SD of 58.2±11.0 weeks in the hospital before maintenance ECT, the average time in the hospital, apart from the periodic 36-hour stay to receive the maintenance ECT, dropped to 3.7±1.1 weeks during the maintenance period. This last figure should be compared to the 27.4±43.0 weeks spent in the hospital during the previous 3 years (Wilcoxon test adjusted to a 36-month period after ECT, $p<0.01$). Similarly, 4.7±1.6 recurrences were observed in the 3 years preceding maintenance ECT and only 1.4±0.6 under maintenance treatment (Wilcoxon test, $p<0.03$), with two (28.6%) of these patients, who often do not respond to treatment, showing no evidence of further mood disorders. Maintenance ECT appears to be a valuable alternative in the treatment of recurrent mood disorders.

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## The Clonidine Test in Posttraumatic Stress Disorder

SIR: Several findings in animals and human beings support the idea of noradrenergic abnormalities in posttraumatic stress disorder (PTSD) (1). The catecholamine-mediated behavioral sequelae of inescapable shock in animals closely parallel the negative symptoms of PTSD in human beings. Fewer platelet $\alpha_2$ binding sites and sustained elevation of urinary norepinephrine levels have been found in PTSD patients. Moreover, antidepressants acting on the noradrenergic system improve PTSD symptoms.

The growth hormone (GH) response to clonidine has already been used as an indirect index of noradrenergic function in various pathological conditions, particularly depressive disorders, with very promising results (2). To our knowledge, this method, however, had never been used in PTSD, and we would like to describe here the results of this neuroendocrine assessment in a PTSD patient before and after successful treatment.

Mr. A, a 20-year-old patient, was hospitalized with a typical case of PTSD, according to the *DSM-III-R* criteria, following a car accident 2 months earlier. He had not received any psychotropic drug for his current symptoms. The traumatic event was reexperienced in recurrent dreams, and the patient persistently avoided stimuli associated with the trauma. Furthermore, persistent symptoms of increased arousal—irritability, difficulty concentrating, and hypervigilance—were present.

Mr. A's clinical condition was assessed with the Impact of Event Scale (3) during his first day of hospitalization, and he received a total score of 45 (intrusive subscale, 20; avoidance subscale, 25). No significant associated depressive features were noted. The clonidine challenge, performed 3 days after admission according to a previously described method (2), showed a blunted GH response (baseline GH level=0.1 ng/ml; peak GH level=4.7 ng/ml).

Implosive therapy was initiated after Mr. A had been taught and had practiced progressive muscle relaxation and guided imagery. Then, the original traumatic scene was presented until satisfactory control of anxiety was achieved. The treatment yielded good improvement of symptoms, with a decrease in the total Impact of Event Scale score to 17 (intrusive subscale, 10; avoidance subscale, 7) after 2 weeks and to 4 (intrusive subscale, 2; avoidance subscale, 2) after 3 weeks. A second clonidine challenge test performed the following week elicited a normal GH response (baseline GH level=0.1 ng/ml; peak GH level=11.1 ng/ml).

Since GH response to clonidine seems to reflect the sensitivity of postsynaptic $\alpha_2$-adrenergic receptors, the initially blunted response noted in our patient supports the idea of decreased noradrenergic sensitivity, which could reflect the down-regulation of noradrenergic receptors. This result is consistent with the decrease in platelet $\alpha_2$ binding sites in PTSD patients described by Perry et al. (4). In addition, the normalization of the clonidine test results after successful therapy suggests that noradrenergic disturbances in PTSD are limited to the pathological period and therefore might represent a state marker rather than a trait marker of PTSD, in contrast to what they indicate in endogenous depression (5). This hypothesis should obviously be tested in a larger group of PTSD patients.

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## Delusions of Pregnancy in a Man

SIR: There have been reports of delusions of pregnancy in men in association with organic cerebral pathology (1) or schizoaffective disorder (2, 3). We should like to report a case of delusions of pregnancy in a male patient without any evidence of such pathology.

Mr. A, a 51-year-old man with a 20-year history of chronic delusional disorder, persecutory type, was admitted to our hospital after having inserted a knife in his anus in order to facilitate delivery of a baby. This patient had been treated for years with depot neuroleptic drugs, but he had interrupted the treatment 3 months before he was admitted. Nine years earlier, he had left the country of his birth, where he was working as a reporter, for political reasons. When he arrived in France, he was married and had a son. His wife did not want to have a second child. A week before his hospitalization, he went to a gynecology clinic; he was excited and expressed the firm belief that he was pregnant. Confronted by physicians' denial of his pregnancy, he exhibited autoaggressive tendencies.

On admission Mr. A complained of abnormal sensations that he misinterpreted as pregnancy: his abdomen was swollen and he felt some abdominal spasms. He thought a baby was moving in his abdomen. He had gained 10 lb, which to him constituted proof of his assumptions. When we pointed out to him that men could not become pregnant, he denied it, explaining that he was "intersexual" (a man and woman at the same time), making a pregnancy possible.

His delusive belief had started after surgical treatment of an anal fistula 4 months previously. He was convinced that a uterus had been grafted into his abdomen during the operation, which took 4 hours. To make certain that he was recovering from the fistula, he had been given a rectoscopic examination. He explained to us that during this investigation, the surgeon had done an anal artificial insemination. Furthermore, he claimed that the depot neuroleptic drugs he took had been used to prepare his body for this pregnancy; he thought they were estrogens. The clue was that during depot neuroleptic treatment, his chest had increased in size and galactorrhea had appeared. In the past he had experienced some homosexual relationships and suffered from difficulties with women, which he related to the abnormal shape of his penis (his genitals were completely normal).

After 4 months of treatment with chlorpromazine, 400 mg/day, the delusion of pregnancy completely resolved. Mr. A continued to receive psychiatric care, and some persecutory delusions still remained.

The number of recorded instances of delusions of pregnancy in men is very small. Organic brain damage plays a strong part in the development of delusions of pregnancy in these patients. However, our patient was free of organic cerebral pathology. He was of normal intelligence, and results of physical and neurological examinations were normal, as were his blood biochemistry and an EEG. There was no history of drug or alcohol abuse and no family history of psychiatric illness or perinatal complications. The delusion of pregnancy constituted a short event in his chronic persecutory type of delusional disorder. This delusion appeared as a secondary phenomenon to misinterpretation of primary somatic sensations.

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## Need for Psychiatric Attention to Greed

SIR: On the fateful day of January 15th, when we were on the brink of war, as I reflected on man's inhumanity to man, the thought crossed my mind that much of it is due to greed. My next thought was, "Where was I when greed was discussed during my 4 years of psychiatric residency and fellowship?"

Thinking that I might have been woolgathering when it was discussed in a seminar or that I missed out on a reading assignment somehow, I decided to rectify matters for myself. I pulled my *Comprehensive Textbook of Psychiatry, Second Edition*, from the shelf and looked up "greed." Not there. Looking in the index of *Noyes' Modern Clinical Psychiatry, Seventh Edition*, for a listing of "greed," I found none. Next, I looked in Hinsie and Campbell's *Psychiatric Dictionary, Fourth Edition*. "Greed" did not exist!

Since my references are not up-to-date, I am writing to learn whether current psychiatric research has remedied what appears to me to be an enormous oversight. If not, perhaps this letter will stimulate some work along this line. The survival of our civilization, such as it is, may depend on it.

Einstein's remark about the need to change our mode of thinking in order to survive in the nuclear age comes to my mind. Understanding greed might be a step in doing so.

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## Dissociation, Borderline Personality Disorder, and Childhood Trauma

SIR: We were very interested to read the article by Susan N. Ogata, Ph.D., and her associates (1) concerning the high prevalence of childhood physical and sexual abuse in inpatients with borderline personality disorder. This finding supports the growing literature which suggests that borderline personality disorder may often be considered a posttraumatic syndrome (2, 3) as well as the finding that a very large percentage of inpatients with traumatic backgrounds have the borderline diagnosis (4). In particular, we were pleased that the presence of derealization was found to be a good indicator of a history of abuse, which supports our finding that dissociative symptoms are correlated with such histories (5).

This confluence of data suggests that dissociation and certain personality disorder traits are both sequelae of childhood abusive experiences. However, for us it raises the question of whether dissociation should be considered part of the borderline syndrome. Particularly with the notion of a dissociative continuum (6), dissociative symptoms in borderline patients may be simply a less severe form of intrapsychic fragmentation than multiple personalities. Thus, many patients with borderline personality may also have an axis I dissociative disorder diagnosis. This is consistent with our clinical experience, which suggests that the dissociative symptoms may respond relatively rapidly to certain abreactive techniques, whereas the personality disorder traits require long-term psychotherapeutic interventions.

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## Dr. Silk and Associates Reply

SIR: We appreciate the response of Drs. Chu and Dill to our article. While we essentially agree with their comments, we caution against too quickly assuming that borderline personality disorder may be a posttraumatic stress disorder (PTSD) or a dissociative disorder. Although it seems clear that some sexually and/or physically abused borderline patients meet the *DSM-III-R* criteria for either PTSD or dissociative disorder, not all abused borderline patients qualify for these diagnoses. Many borderline patients fail to meet criterion C for PTSD (persistent avoidance of stimuli associated with the trauma or numbing of general responsiveness). In fact, many of them seem to repeat the trauma, through self-destructive acts and/or masochistic and unstable interpersonal relationships (although these are not always willful or wholly conscious). While dissociative disorders may be diagnosed in patients with episodes of depersonalization or derealization that are frequent and severe enough to cause marked distress, we think it premature to conclude that all borderline patients who experience dissociation have a less severe form of multiple personality disorder. Gunderson and Elliott (1) pointed out that similar symptoms may arise from different etiologies, and dissociative phenomena, which are seen in a variety of psychiatric disorders and among nonpatients as well (2), may tell us very little about the etiology or pathogenesis of the personality disorder as a whole. Our study showed that in carefully screened *borderline* patients, derealization was the best predictor of sexual abuse, but the study said nothing about dissociative experiences in other patients. In the study by Drs. Chu and Dill, patients who had experienced both sexual and physical abuse had the highest scores on the Dissociative Experiences Scale, but patients with neither sexual nor physical abuse had higher scores than patients who had experienced sexual abuse alone.

In the *DSM-IV* axis II work group, there is growing support for including in the set of criteria for borderline personality disorder a criterion related to transient psychotic-like experiences that would encompass depersonalization and derealization as well (J.G. Gunderson, personal communication). What to us is most exciting, however, is the recent increase in empirical studies directed at a better understanding of dissociative phenomena. However, until we have more information, we reserve judgment about what clinical techniques would be most favorable for borderline patients, and we caution against a too rapid uncovering of repressed memories, which may have been repressed for quite adaptive reasons.

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### Borderline Personality Diagnosis in Children and Adolescents

SIR: The striking findings of Pamela S. Ludolph, Ph.D., and associates (1) in their study of the borderline diagnosis in adolescents are an important contribution to the growing literature that documents abuse and neglect by caretakers in the developmental histories of patients with borderline personality disorder (2, 3). The authors compared and contrasted their findings with those of our study "An Examination of the Borderline Diagnosis in Children" (4). In our study we used the Diagnostic Interview for Borderlines (DIB) adapted for retrospective diagnosis by chart review, which we had modified slightly for use with children, to diagnose a group of 86 hospitalized 6- to 12-year-old children as either having or not having borderline personality disorder. We then examined differences between the borderline and nonborderline groups on a number of nondiagnostic variables.

It is understandable that Dr. Ludolph and associates compared the two studies, because they too used the DIB (though prospectively) and examined similar nondiagnostic variables. However, we are concerned that it may be misleading to compare the results as they did. Our study was of a group of predominantly male (72%) children who were 6–12 years old. Their study was of female subjects only, and the subjects were adolescents aged 14–18 years. It is helpful, and not surprising, to have data that support the use of the DIB and the borderline diagnosis for female adolescents, but the data do not shed light on the question of whether the borderline diagnosis is a useful one for children. Although we understand that the authors were not claiming to validate the borderline diagnosis for children, their focus of comparison with our study could give a reader the impression that their results somehow contradict ours. In fact, the relative scarcity of male adolescents with borderline personality disorder noted by the authors may indicate that the borderline syndrome in male children results in a quite different—and nonborderline—outcome, even by the time they are adolescents.

In other words, despite the similar research design, the fact that the studies had different subjects makes it difficult to interpret apparent similarities and differences in the results. This in no way detracts from the major finding of the study, namely, that the adolescent female subjects with borderline personality disorder had traumatic histories.

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### Dr. Ludolph and Dr. Westen Reply

SIR: We thank Drs. Greenman and Gunderson for their comments on our article and regret any implication that our results contradict theirs. Our intent in mentioning their study was to credit Drs. Greenman and Gunderson for aspects of our research design and then to contrast our findings with respect to the age of the subjects. This comparison suggested that an adult-type borderline profile can clearly be found in adolescent girls, whereas this appeared somewhat less true for the group of younger children they studied. Extrapolating a little further, it may be that the adolescent (and adult) diagnosis of borderline personality disorder is not continuous with the childhood diagnosis; this is also our clinical impression. Thus, we fully agree that the borderline syndrome in male (or female) children may result in a different outcome as the children mature. We look forward to the result of longitudinal investigations, such as that begun by Drs. Greenman and Gunderson with their study, to answer this important question.

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### Comments on Hypnotizability and Dissociation

SIR: Fred H. Frankel, M.B., Ch.B., D.P.M., urged restraint in the use of the term "dissociation" in his recent review of the subject (1). While caution is always prudent, Dr. Frankel seems to have ignored important components of the literature, many of them published in the *Journal*, which might serve to temper his conclusions.

Dr. Frankel wondered why there is preferential interest in what he called the "passive mechanism" of dissociation rather than the "active mechanism" of repression. A defense mechanism that repeats the physical experience of enforced passivity in psychological terms might be especially appropriate to posttraumatic symptoms. Furthermore, dissociative phenomena demonstrate that coherence of identity is not an automatic given from which components may be subtracted. Rather, an integrated identity is an accomplishment that is subject to disruption through trauma, hypnotic influences, or disjunctions in information-processing strategies (e.g., explicit versus implicit memory) (2).

Dr. Frankel cautioned against overinterpreting the relationship between hypnotizability and dissociation or other forms of clinical behavior while at the same time he defended his observation of a link between high hypnotizability and phobic symptoms. Although hypnosis has elements other than dissociation (e.g., absorption and suggestibility), it has long been recognized as a formal means of eliciting dissociative phenomena. Dr. Frankel challenged our study supporting the connection between hypnotizability and dissociation. We demonstrated significantly higher hypnotizability among 65 Vietnam veterans with posttraumatic stress disorder than in various other groups of patients and normal subjects. He implied that the results of our study are contradicted by an unpublished report by Sexton et al. on the hypnotizability of sexually abused individuals. While one cannot be sure what those authors found, it appears to be in an entirely different population. Furthermore, Dr. Frankel omitted mention of a study by Stutman and Bliss (3), published in the *Journal* before our own study, which also demonstrated higher hypnotizability among Vietnam veterans with posttraumatic stress disorder.

Dr. Frankel criticized the Dissociative Experiences Scale. It has performed an important service by quantifying dissociative events and attempting to construct a continuum between normal and pathological experience. However, if one is to criticize it, at least one might cite the fascinating finding by Herman et al. (4), which showed a strong relationship between reports of abuse in childhood and scores on the Dissociative Experiences Scale in a group of borderline patients. Furthermore, in the same issue of the *Journal* in which Dr. Frankel's article appeared, Chu and Dill (5) reported higher Dissociative Experiences Scale scores and more dissociative symptoms among psychiatric patients who had been physically and sexually abused.

The study of dissociation is a rich and complex area with accumulating evidence which suggests that some early observations linking trauma and dissociative symptoms were correct. This in turn provides a systematic rationale for the use of techniques such as hypnosis as part of an approach to psychotherapy that acknowledges and helps patients deal with traumatic origins of symptoms. While we certainly would not urge Dr. Frankel to throw caution to the winds, we would ask him to assess more carefully the prevailing winds.

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## Dr. Frankel Replies

SIR: It is precisely because of a careful assessment of the prevailing winds that I felt constrained to draw attention to the risks involved in the ubiquitous references to dissociation and to the current semantic juggling, all in the absence of clearer conceptualization.

The assertion by Drs. Spiegel and Cardeña that a defense mechanism that reflects the physical experience of enforced passivity in psychological terms might be especially appropriate to posttraumatic symptoms is a case in point. Intellectually tidy and entirely appropriate and helpful in conducting therapy, it is also a clear example of how a metaphor, useful in the practice of psychotherapy, shapes the concepts and begins to achieve the quality of fact in the explanation of a problem and its treatment—an unfortunate trend in several current systems of hypnotherapy. I have reported (1) on a patient who recalled that as a boy he had learned, he knew not where, that when he saw punishment coming his way, he could turn a switch somewhere within himself which helped him block out the feeling and make it painless. Terr (2) reported similar cases. Is this redirected attention, information-processing strategy, denial, or passive dissociation?

Far from defending my own findings while undermining those of others, as Dr. Spiegel and Dr. Cardeña seem to imply, I clearly stated that the findings of Council et al. (3) have raised interesting questions about the influence of the context in which *all* hypnotizability ratings are carried out. These authors pointed out that if hypnosis is emphasized elsewhere in the context of the relationship, the subjects achieve higher scores. While this finding has still to be replicated by others, it does encourage a more cautious interpretation of all clinical hypnotizability studies and the acknowledgment of other contributory factors such as suggestion.

The thrust of my argument was clear. I would draw the attention of Drs. Spiegel and Cardeña to my point that in the current understanding of dissociation, clarity is conspicuous by its absence. Dramatic amnesia and clear-cut changes in or discontinuity of consciousness, control, or identity make compelling arguments for the presence of dissociation. Milder experiences included in the Dissociative Experiences Scale that have some resemblance to dissociation might well reflect qualitatively very different factors, such as recall, attention, imaginative capacity, attribution, and control. In my view—a view shared by many—the concept of dissociation has been elaborated in recent years to an exaggerated degree, artfully buttressed to a large extent by the findings in hypnosis research. Instead of capturing dissociative elements in the fine brushwork, several authors have preempted the canvas with broad strokes. Character pathology, object relations, and the demands of investigative questioning and the clinical situation have been shunted aside. The result is an unfortunate oversimplification of the complexity of human behavior and human suffering. I suggest to Drs. Spiegel and Cardeña that the prevailing winds directing their sails might be largely man-made.

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## Monosymptomatic Hypochondriacal Psychosis and AIDS

SIR: Valerie F. Holmes, M.D. (1) reported a hitherto unrecorded association between AIDS and the unusual psychiatric symptom of delusional parasitic infestation. Delusional parasitosis is indeed the most common presentation of the wider psychiatric disorder known as monosymptomatic hypochondriacal psychosis. However, this symptom may occur as the principal manifestation of a separate underlying organic disorder, either psychiatric or nonpsychiatric. Disorders predisposing to the development of delusional parasitosis are commonly associated with abnormal cutaneous sensory perception, particularly phenomena of the pruritic or paresthetic type (2). The misinterpretation of peripheral perceptions lies close to the core of hypochondriacal somatic symptoms. The history of Dr. Holmes's patient included liver disease, chronic anemia, and substance abuse—all conditions previously reported in association with disordered tactile experience and delusional parasitosis (2).

With these observations in mind, it may not therefore be necessary to postulate a direct link between AIDS and the symptom of delusional parasitosis. However, it is interesting to note that paresthetic phenomena have been recorded as part of the presentation of AIDS (3), and this may constitute the pathological link between the two disorders in Dr. Holmes's patient. Subsequent reports of this association will certainly be awaited, since at this stage it may be premature to add AIDS to the already lengthy list of organic disorders that can include the symptom of delusional parasitosis in their presentation.

We are pleased to learn of this patient's response to the diphenylbutylpiperidine neuroleptic pimozide, corroborating our own experience with delusional parasitosis (4). It should be noted that pimozide may often be therapeutically effective irrespective of the pathological basis of the disorder, be it associated with monosymptomatic hypochondriacal psychosis or a discrete primary organic or psychiatric disorder. Pimozide's mode of action in the treatment of delusional parasitosis may reflect not only its specificity as a dopamine receptor antagonist (other neuroleptics are less predictably effective) but also its unusual property of central opiate antagonism, possibly resulting in the suppression of pruritic and related sensory phenomena (5).

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## Dr. Holmes Replies

SIR: Dr. Reilly and Mr. Batchelor are correct in stating that there are a number of conditions that can predispose to an organic delusional disorder. Cummings (1) cited an impressive list of organic disturbances that may produce delusions and commented that delusions seem to be more evident in disorders associated with limbic and subcortical dysfunction as opposed to disorders involving the neocortex. Since HIV involvement of the CNS has been described as a subcortical process (2), it is less curious that a delusional disorder may become manifest during the course of this illness. It is also true that sensory polyneuropathies are the most common peripheral neuropathies encountered among patients with HIV infection (3), although formication has not been frequently described.

I would not agree that pimozide's property of opiate antagonism is unusual, however, since multiple classes of neuroleptics, including butyrophenones, benzimidazolinones, tetrahydroindolones, and phenothiazines, have all been shown to have moderate to high affinities for the so-called sigma (σ) opiate receptor (4). Perhaps more important, more recent studies have not only called into question the validity of using the term "opiate" in describing the σ receptor—since it has been shown to have properties very distinct from those of the standard opiate receptors μ (morphine), κ (ketocyclazocine), and δ (enkephalin)—but suggest that this particular receptor may play a significant role in the abnormal involuntary movements that occur with neuroleptic therapy.

Walker et al. (5) found that the brainstem nuclei which control the muscles most commonly involved in neuroleptic-induced movement disorders, such as the hypoglossal, facial, oculomotor, abducens, trochlear, and trigeminal motor nuclei, are especially rich in these receptors. This coincides anatomically with the commonly seen abnormal buccal, oral, lingual, and facial movements as well as with oculogyric crisis. To further support this hypothesis, these authors found that clozapine, which reportedly does not cause movement disorders in human beings, also does not bind to the σ receptor. These findings are certainly intriguing and may help to define better the roles of neuroleptics, neurotransmitters, and receptors in psychiatric disorders.

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## Thyroid Function and Postpartum Depression

SIR: Paul Claman, M.D. (1) recently took issue with Michael J. Gitlin, M.D., and Robert O. Pasnau, M.D. (2) for failing to recognize that "postpartum thyroid dysfunction is an important cause of late postpartum depression." He recommended "a simple thyroid-stimulating hormone (TSH) screen to rule out transient hypothyroidism as the cause of postpartum depression." In fact, it is not yet proven that thyroid dysfunction is an *important* cause of postpartum depression, and the investigation of thyroid function after delivery is not always as simple as suggested.

My colleagues and I previously showed (3) that women with postpartum affective psychoses had a no greater prevalence of thyroid dysfunction than matched postpartum control subjects and that both the patients and the control subjects had altered thyroid function indexes ($T_4$ levels elevated, $T_3$ resin uptake levels low) for approximately 3 weeks following delivery. More recently, Harris et al. (4) demonstrated an association between autoimmune thyroiditis accompanied by thyroid dysfunction (both hypothyroidism and hyperthyroidism) and postpartum depression, as measured by the Raskin but not the Edinburgh and Montgomery-Åsberg depression rating scales. This finding clearly requires further study with a larger sample.

Meanwhile, thyroid function should be assessed in women with postpartum depression, bearing in mind that results of these tests frequently do not return to prepregnancy baseline levels until approximately 3–4 weeks after delivery. While I agree that thyroid dysfunction should be considered in the individual woman with postpartum depression, the role of the thyroid as an important cause of this condition is not yet established.

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## Dr. Claman Replies

SIR: I appreciate the interest Dr. Stewart has shown in my letter. I agree completely with the points she has made and again reiterate the importance of measuring the serum TSH level to rule out transient hypothyroidism as the cause of *late* postpartum depression (i.e., occurring months following delivery).

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## Community-Based Care in Western Massachusetts

SIR: The two-part article by Jeffrey L. Geller, M.D., M.P.H., and colleagues (1, 2) on the impact of *Brewster v. Dukakis* is excellent. However, as an active member of the Alliance for the Mentally Ill of Western Massachusetts, for which I lead the Northampton family support group, and as a family member familiar with mental health services in the Franklin/Hampshire area of region I, I would like to call attention to some points the article failed to mention.

In part II the authors stated that "region I under the terms of the Northampton Consent Decree . . . has met virtually all of the requirements of a comprehensive system of community-based care." I agree that most of the types of services needed are in place, but it is readily apparent that the supply is inadequate to meet the needs of all seriously mentally ill persons in the region. Patients who have been in private hospitals but not in Northampton State Hospital are not included in the Northampton Consent Decree. They usually have to wait many weeks to receive outpatient treatment. Quite often this wait precipitates a crisis.

According to the contract of the Franklin/Hampshire Mental Health Center, the emergency services have "a primary goal of reducing the number of state hospitalizations." When hospitalization is required, this agency first attempts to find a bed in a private hospital. If this is achieved, it has the effect of preventing the patient from becoming a *Brewster* client and thus gaining eligibility for community residential care.

According to the Department of Mental Health's 1989 Comprehensive Mental Health Service Plan, on the basis of population figures and demographics, there are presumed to be 6,039 adult priority clients in region I. These priority clients are defined as persons "who are seriously or long-term mentally ill, who have a substantial disorder of thought, mood, perception, or memory which grossly impairs judgement, behavior, capacity to recognize reality or the ability to independently meet life support needs of food, shelter, clothing, income and health care." The total number of beds with some degree of supervision available to such persons is 731. This number is inadequate even for all of the *Brewster* clients, some of whom remain in the state hospital months longer than necessary because there is no suitable bed available in the community. In July of 1989 there were 48 patients in the hospital awaiting community placement, yet only two were placed in residences with some supervision.

Some of the priority clients are homeless, some are living alone in constant danger of relapse, and some are cared for by their families at great financial and emotional cost. In many cases this lack of appropriate community care precipitates readmissions to the hospital.

During fiscal year 1989 Northampton State Hospital discharged 590 patients directly to the community. Of these, 233 were discharged to self-care, 136 to their families, 23 to friends or boardinghouses, 55 to respite or emergency shelter, and 143 to group homes or apartments with some supervision. During that year the recidivism rate at the hospital averaged 72.6% (figures supplied by the hospital to the Citizens' Monitoring Committee).

It is true that a great deal has been accomplished during the period the consent decree has been in effect. However, on the basis of my personal experience and experiences related to me by other family members and consumers, I cannot agree that western Massachusetts has even come close to meeting "the requirements of a comprehensive system of community-based care."

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## Dr. Geller and Dr. Fisher Reply

SIR: We thank Ms. Bouricius for both her careful attention to our research and her complimentary comments on our article. Further, we applaud her efforts, and those of the Alliance for the Mentally Ill of Western Massachusetts, to address issues pertaining to the Northampton Consent Decree. Two themes Ms. Bouricius raises warrant further discussion.

Ms. Bouricius outlines one outcome for patients who are not admitted to the state hospital but are directed to private hospital beds when inpatient treatment is warranted: they do not become entitled to services that would have accrued to them if they had been admitted to the state hospital. One of us (J.L.G.) recently discussed the effects of diversion from state hospital admission in region I (1). Ms. Bouricius makes another point that underscores what has been all but ignored for the past 3 decades: services for any individual with serious and persistent mental illness should be determined by clinical needs, not by a confused formula driven by the serendipity that resulted in the individual's past use (or nonuse) of the public system of care.

Ms. Bouricius's second theme addresses the adequacy of community-based services in region I. We must point out that her quotation from our article regarding region I's having met the requirements of a comprehensive system of care was not our assertion but, rather, a statement referenced to the attorney who brought the class action suit, *Brewster v. Dukakis*, that led to the Northampton Consent Decree (2).

The question of adequacy of resources, particularly with regard to residential programs, is nonetheless an interesting one. What is adequate? One way to address this question is to compare resource levels in region I with those elsewhere. According to 1985 data published by the National Institute of Mental Health (3), Massachusetts spent $6.25 per capita on residential programs. This ranked second in the nation only to Minnesota, which spent $8.96. In fiscal year 1986 (July 1, 1985 to June 30, 1986), budgetary data furnished by the Massachusetts Department of Mental Health show that per capita funding for residential programs in region I was $15.14. If region I were a state, it would rank first among all states in per capita expenditure for state-supported residential programs, outspending Minnesota by about 68%. This level of funding has not only created a large supply of beds but has also provided for a continuum of residential services far more extensive than that developed in most areas. For example, region I has available 159 "level I" beds, which are costly, staff-intensive settings for patients needing high levels of supervision. A neighboring region in Massachusetts currently has no such beds at all. The entire state of Massachusetts outside region I, with 86% of the population of the state, has only 145 of these beds, or 48% of the total number of level I beds statewide.

The persistence of the problems Ms. Bouricius outlines in the context of arguably the best-funded community residential program anywhere in America raises questions about whether these problems would be ameliorated by creating even more residential beds. If a state were to double its level of funding for residential programs, would the use of its state hospitals be cut in half? Massachusetts' experience with the Northampton Consent Decree suggests that it would not. Even if it were, would a dollar spent in the community ever save a dollar in the hospital? Would the quality of life of those with serious and persistent mental illness necessarily be improved by the changed locus of care? These questions are central issues in the framing of future mental health policy. The Northampton Consent Decree and the community mental health care system of western Massachusetts offer an unprecedented opportunity to examine and debate these basic questions.

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## Efficacy Research and Psychodynamic Psychiatry

SIR: Alan A. Stone, M.D. (1) raised wise doubts about whether efficacy research is sufficiently advanced that it can be used to decide between the competing clinical paradigms of the science of mind, and perhaps even world views, implicit in the *Osheroff v. Chestnut Lodge* case. At the risk of redundancy, I wish to amplify these doubts with the following reflections.

More than a decade of engaging in a dialogue about utility assessment does not leave me with any clearer understanding of the commensurability of such values as 1) autonomy achieved through insight and 2) the kind of freedom from depression that can be psychopharmacologically induced. Moreover, there is good reason to believe that how much we value such functions in a given case is profoundly dependent on the method and context of measurement as well as the person whose values are being measured (2).

It is understandable that outcome studies tend to be primarily concerned with assessing easily measurable, relatively short-term outcomes such as improvement in sleep and neglect longer-term, less easily quantifiable outcomes such as autonomy. However, even if methods of measurement for these latter variables come to be developed, there is no reason to believe that methods for measuring how much we value such "soft" variables can be as easily developed. In fact, what constitutes validity for such utility measures is open to debate. Shifting the debate about efficacy from courtroom trials to clinical trials is not likely to mend the rifts in clinical understanding that are at the heart of *Osheroff v. Chestnut Lodge*. Elsewhere my colleagues and I have argued that there is ample reason to consider that psychodynamic psychiatry can itself contribute to perfecting these very methods of utility assessment (3). Before the clinical trial becomes the court of first resort for settling these clinical controversies, perhaps psychodynamically informed research will have to make a much-needed contribution to the still infant science of utility assessment.

On another note, I do not believe that the different psychological capacities, such as memory, concentration, and autonomy, are so selectively or exclusively enhanced by one form of treatment as to preclude the integration of psychodynamic insight with psychopharmacological intervention. Whether either or both are used, a psychodynamically informed approach to informed consent as a *process* can help to increase the patient's sense of autonomy (4). As for turning to the courts as a first resort, Dr. Stone suggested the sensible alternative of a clinical consultation. Depending on the clinical issues, two other consultations may be in order. 1) A forensic psychiatric consultation to assess a patient's capacity to engage in the risk-benefit dialogue regarding treatment alternatives can take the burden of competency assessment off the treatment alliance (5). 2) A consultation with a psychiatrically informed ethicist can bring to light covert value investments that too often drive the dialogue about treatment choices. Such consultations can prevent those misunderstandings of a patient's capacities or values which often lead to regret, recrimination, and even a malpractice suit in the event of a tragic outcome (6).

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*Reprints of letters to the Editor are not available.*

# Corrections

In the letter to the Editor "Efficacy of Psychotherapy" from Victor Bloom, M.D. (December 1990 issue, p. 1700), the last sentence should have stated that Dr. Bloom "has practiced and taught for 30 years."

In the March 1991 issue, only one author, Russell T. Joffe, M.D., was given for the letter to the Editor "Thyroid Function and Phototherapy in Seasonal Affective Disorder" (p. 393). Anthony J. Levitt, M.D., and Sidney H. Kennedy, M.D., should have been listed as coauthors of this letter.

In the paper "Continuous Versus Targeted Medication in Schizophrenic Outpatients: Outcome Results" by William T. Carpenter, Jr., M.D., et al. (September 1990 issue, pp. 1138–1148), there was an error in calculating dose levels for patients. The new table 3, below, contains the corrected doses and corrected analyses. These changes do not affect data interpretation or any of the conclusions of the study.

**TABLE 3. Average Neuroleptic Dose Levels of Schizophrenic Outpatients Given Targeted or Continuous Medication for 2 Years**

| | Average Dose Level[a] | | | | | | |
|---|---|---|---|---|---|---|---|
| | Targeted (N=57) | | Continuous (N=59) | | ANOVA | | |
| Period | Mean | SD | Mean | SD | F | df | p |
| Entire study | 1.22 | 0.79 | 1.71 | 0.83 | 10.35 | 1, 114 | 0.002 |
| All days as outpatient | 1.00 | 0.75 | 1.64 | 0.85 | 18.26 | 1, 114 | 0.0000 |
| All days of drug treatment, except during hospitalizations | 2.18 | 0.77 | 1.87 | 0.76 | 4.53 | 1, 107 | 0.04 |

[a] 0=no drug, 1=low dose, 2=moderate dose, 3=moderately high dose, 4=high dose.

# Position Statement on School-Based Health Clinics

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*This statement was proposed by the Council on Children, Adolescents, and Their Families.[1] It was approved by the Assembly of District Branches in November 1990 and by the Board of Trustees in December 1990.*

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The American Psychiatric Association (APA) recognizes the valued place of the school-based health clinic in elementary, middle, intermediate, and senior high schools. These clinics have been an important part of supporting better health for American children and adolescents in public schools for over two decades. They offer a significant benefit to child and adolescent mental and physical health, particularly for young people who might not otherwise receive needed assistance for serious health problems. Since they are located within the daily environment of most young persons, the clinics lessen economic and psychological barriers to proper medical care. Despite these unique advantages, it has been unfortunate that mental health assistance has not been as readily available in most clinics as have nonpsychiatric medical services.

APA urges that ways be found to increase the availability of psychiatric participation. At least 20%, and in some studies up to 60%, of the adolescents seeking services have been found to have mental health problems needing treatment. Many live in disadvantaged families who also need attention and may need transportation to receive the services. Some successful financing arrangements for school consultation have involved funds from the school districts themselves (general funds or federal-state funding under PL-94-142, the Education for All Handicapped Act) and funds that have been directed at youth problems, such as suicide and substance abuse. To fully use the opportunity for preventive service available in these clinics, the child and adolescent psychiatrist should be a member of the team alongside the other medical specialties and other mental health professionals.

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[1] The Council on Children, Adolescents, and Their Families includes Lawrence A. Stone, M.D. (chairperson), John Guy Looney, M.D. (vice-chairperson), Irving Philips, M.D., Mohammad Shafii, M.D., Elva O. Poznanski, M.D., Cynthia Darnell Barnes, M.D. (observer-consultant), Gloria Faretra, M.D. (consultant), Michael E. Fishman, M.D. (consultant), David Burton Pruitt, M.D. (consultant), Fred Gottlieb, M.D. (Board liaison), William M. Womack, M.D. (Assembly liaison), George Richard Athey, M.D. (APA/Burroughs Wellcome Fellow), and Alice R. Brams, M.D. (APA/NIMH Fellow).

# Interim Guidelines for Occupational HIV Exposure Protocols and Protections

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*This statement was proposed by the Commission on AIDS*[1] *and is based on guidelines originally drafted by the San Francisco Medical Society. It was approved by the Assembly of District Branches in November 1990 and by the Board of Trustees in December 1990.*

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Occupational risk of HIV infection for health care workers is now a documented fact. Research continues into the true degree of risk for various health care occupations and the optimal tactics for minimizing that risk and managing cases of actual exposure. However, some standards in these areas are becoming widely accepted and should be implemented wherever health care workers are at occupational risk for HIV (as well as for other blood-borne and body-fluid-borne pathogens). The following recommendations are offered as minimum guidelines for health care settings operating in this era of occupational HIV risk. For specific guidelines regarding infection control and risk management consult relevant references and organizations (1–8).

1. All health care personnel at potential risk of occupational exposure should receive intensive and continuing education about the degree of risk entailed, procedures for minimizing risk, and resources available to them for dealing with individual concerns and actual cases of exposure. Such training and education should be mandatory for anyone working or training in hospitals and other institutions; individuals working in non-institutional settings, such as the home or other nursing settings, should also receive such education.

2. All hospitals and other health care institutions should have explicit policy regarding occupational risk of HIV and should provide the physical and personnel resources necessary to implement and adhere to those policies. Confidentiality and potential discrimination are at issue, in addition to infection control and health care needs. HIV-specific policies should be in accord with relevant professional and governmental guidelines, including those of medical and hospital associations and the U.S. Occupational Safety and Health Administration (OSHA).

3. Each health care institution should have in place a detailed protocol for responding to actual cases of exposure in a timely manner, covering professional counseling, access to state-of-the-art therapeutic responses to exposure, and appropriate medical and psychiatric follow-up resources. Where such programs are not provided in an individual institution, arrangements for access to such programs should be made through readily accessible referral sources.

4. All counseling and testing of health care personnel and patients regarding occupational risk and actual exposure should be provided under the explicit informed consent and confidentiality protections provided for by law and established medical standards of practice. In situations where worker confidentiality may pose potential conflicts, the risks and benefits of each course of action should be fully explained to the worker so that an informed choice may be made.

5. Employee benefits, such as workers' compensation, should adequately reflect the recognition of HIV as an occupational risk and the immediate and long-term health care and financial needs of workers who are occupationally exposed and infected. These benefits should also cover health care professionals in training. Every health care worker or trainee should be fully informed as to the extent and limitations of occupational insurance and disability coverage as they pertain to HIV exposure and infection.

6. Health care employees at risk of occupational HIV infection should have adequate and explicit legal protections against discrimination arising from their risk of occupational infection.

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[1] The Commission on AIDS includes James Krajeski, M.D. (chairperson), Jeffrey Akman, M.D., Alexandra Beckett, M.D., Francisco Fernandez, M.D., Janice Hutchinson, M.D., Joyce Johnson, D.O., Eric Kaplan, M.D., Robert Kertzner, M.D., Stuart Nichols, Jr., M.D., David Rosmarin, M.D., Jackie Etemad, M.D., Simon Auster, M.D. (corresponding member), Ruth Herman, M.D. (APA/Burroughs Wellcome Fellow), Eric Bing, M.D. (APA/NIMH Fellow), Douglas Sargent, M.D., J.D. (Board liaison), and James Nininger, M.D. (Assembly liaison).

# Interim Guidelines Regarding Psychiatrists Who Are HIV Infected

*This revision of the statement originally adopted in September 1988 was proposed by the Commission on AIDS.*[1] *It was approved by the Assembly of District Branches in November 1990 and by the Board of Trustees in December 1990.*

## INTRODUCTION

HIV-infected individuals must be treated with compassion and with due respect to rights, privacy, and confidentiality. The available evidence and the current guidelines of the U.S. Centers for Disease Control (CDC) suggest no indication for mandatory HIV testing for all physicians. However, because of the physician's professional obligation to do no harm, guidelines are needed in the event that psychiatrists are unable to perform professional duties because of HIV disease. Psychiatrists, like all physicians, should be aware of and comply with the CDC guidelines for preventing transmission of infection with HIV. Clinical evidence indicates that HIV infection is not spread by casual contact. The clearly defined modes of transmission are direct exposure to HIV-infected blood and direct exposure to HIV by sexual contact.

State laws and regulations vary in their public health reporting requirements and in the obligations imposed on physicians regarding colleagues about whom questions of competency exist. Psychiatrists must be aware of the laws in the jurisdictions in which they practice.

## CLINICAL COMPETENCY

Recognition of impairment of clinical competency resulting from any illness should be the responsibility of the individual treating the psychiatrist, as well as supervisors, colleagues, and family. Restriction of clinical privileges on the basis of HIV infection alone is clearly unwarranted. When observations of the psychiatrist's behavior indicate impaired clinical competence, the American Psychiatric Association (APA) "Guidelines to District Branch Impaired Physician Committees" should be followed and appropriate authorities notified.

## CONFIDENTIALITY

Reporting to public health authorities of HIV infection in psychiatrists should be no different from that for other infected individuals. All reporting should maintain an individual's rights to privacy and confidentiality. APA's guidelines relating to confidentiality and disclosure (1) apply to psychiatrists who are HIV infected, as well as other infected individuals.

## DISCRIMINATION

Action against an otherwise qualified individual in licensing, hospital privileges, or admission to medical training programs on the basis of HIV status is discriminatory and in violation of federal law and APA policy.

### *Licensing*

Psychiatrists with HIV infection should be under the same licensing requirements as other psychiatrists with psychiatric or other medical conditions. There is no indication for mandatory HIV testing for physician licensure. Denial or suspension of the affected psychiatrist's license on the basis of HIV infection alone should not occur.

### *Hospital Privileges and Admission to or Promotion in Psychiatric Residencies*

There is no indication for mandatory HIV testing for hospital privileges or for admission to or promotion within psychiatric residencies. HIV infection alone is not grounds for exclusion from residency or hospital privileges. Psychiatric or other medical impairment, on the other hand, needs to be evaluated.

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[1] The Commission on AIDS includes James Krajeski, M.D. (chairperson), Jeffrey Akman, M.D., Alexandra Beckett, M.D., Francisco Fernandez, M.D., Janice Hutchinson, M.D., Joyce Johnson, D.O., Eric Kaplan, M.D., Robert Kertzner, M.D., Stuart Nichols, Jr., M.D., David Rosmarin, M.D., Jackie Etemad, M.D., Simon Auster, M.D. (corresponding member), Ruth Herman, M.D. (APA/Burroughs Wellcome Fellow), Eric Bing, M.D. (APA/NIMH Fellow), Douglas Sargent, M.D., J.D. (Board liaison), and James Nininger, M.D. (Assembly liaison).

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*Special Articles*

# Prodromal Symptoms in Affective Disorders

**Giovanni A. Fava, M.D., and Robert Kellner, M.D., Ph.D.**

*Objective: The aim of this paper was to review the clinical and conceptual implications of the studies investigating prodromal symptoms of mania, depression, and panic disorder. Method: Twenty-four studies specifically addressing the issue of prodromal symptoms in mood and anxiety disorders were selected by computer search (Medline) and manual search of Index Medicus and the psychiatric literature. Results: Most of the studies have described a prodromal phase in the development of mania, depression, and panic attacks. Conclusions: The appearance of prodromal symptoms may precede the full syndrome by weeks or months; if these symptoms are detected, recurrences of affective disorders (bipolar illness, unipolar depression, panic disorder) could be treated earlier and perhaps more effectively.* DSM-III *has emphasized the traditional clinical syndromes and cross-sectional descriptions. Appraisal of prodromal and residual phases may complement this approach. The longitudinal study of prodromes, the fully developed disorder, and residual states calls for an assessment of personality, neurotic traits, and their interaction in the evolution of affective disorders.*

(Am J Psychiatry 1991; 148:823–830)

The term "prodrome" derives from the Latin word *prodromus,* which in turn stems from the Greek *prodromos*. It indicated the forerunner of an event (e.g., a race). In medicine, prodromes can be identified with the early symptoms and signs that differ from those of the acute clinical phase. The prodromal phase connotes a time interval between the onset of prodromal symptoms and the onset of the characteristic manifestation of the fully developed illness. Infectious diseases provide simple models for the difference between the phases. With some infections, such as acute upper respiratory tract infections, the onset of the illness is abrupt and prodromal symptoms last only a few hours. In others, such as tuberculous meningitis, the prodromal phase can be long. The latter is an example of a striking difference between prodromes that may be vague, with symptoms such as fatigue and anorexia, whereas the full manifestations are characteristic of a catastrophic intracranial disease.

Appraisal of prodromal symptoms has been of importance in clinical medicine for many progressive, dangerous, and treatable diseases in which early detection and timely treatment are crucial. Research on prodromal symptoms in psychiatry has been largely anecdotal and a relatively rare topic of systematic study. An exception concerns schizophrenia (1–5), in which appraisal of prodromal symptoms appeared to be important for early therapeutic intervention to prevent the development of full-blown psychotic episodes (6, 7).

The aim of this article was to survey prodromal symptoms in affective disorders. The term "affective disorder" includes in this study both mood and anxiety disorders. This paper consists of three parts: the methodology of the study of prodromal symptoms, a review of the literature on three disorders for which a few studies are available (bipolar disorder, unipolar depression, and

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panic disorder), and a discussion of the clinical and theoretical implications of this topic.

## METHODOLOGICAL ISSUES

Several methodological problems are involved in the exploration of affective prodromes. These include definition, measurement, assessment, and constructs with blurred boundaries.

### *Definition*

The first difficulty lies in the determination of onset of the acute phase of illness. The appearance of specific symptoms may be chosen as an anchor point (e.g., the first onset of panic attacks). Alternatively, a criterion of severity may be selected. Subotnik and Nuechterlein (4), for instance, used a rating of 6 or 7 (severe or extremely severe) on selected items of the Brief Psychiatric Rating Scale (BPRS) (8) to define psychotic relapse. The choice of the end point of the prodromal phase differs with the disorder; for example, panic disorder has a dramatic onset; in a depressive episode that becomes gradually worse over several months, a cutoff point of severity or impairment needs to be chosen. A second arbitrary decision involves the time span—in a retrospective design—when prodromal symptoms are investigated (e.g., 6 months before the first panic attack). Finally, the differentiation between prodromal and residual symptoms—as discussed in detail later—may confound, at times, the determination of the beginning of the prodromal phase.

### *Measurement*

Clinical history should be the basic method for appraisal of prodromal symptoms in psychiatry and other branches of medicine. Several studies of affective disorders relied on exploration of symptoms by clinicians, whereas rating scales ensured the exploration of a range of phenomena as well as comparability of findings across studies. The need for their reliability and validity is self-evident. However, since prodromal symptoms are frequently milder than those of the full clinical syndrome, the capacity of the scale to measure small increments or small changes near the normal end of the spectrum becomes important. The ability of a rating or self-rating scale to discriminate between different groups of patients suffering from the same illness (e.g., depressed inpatients and outpatients) and to reflect changes in experiments in therapeutics such as drug trials in which the drug effects are small may indicate its degree of sensitivity (9). Feinstein (10) regards such discriminating properties of the desired distinctions as crucial components of the sensibility of a scale, together with characteristics such as simplicity, clinical justification and applicability, and clarity of instructions. In the study of prodromal symptoms, sensitivity and sensibility are desirable properties. However, the higher the sensitivity of a rating scale, the higher the likelihood of false positive findings in terms of detection of symptoms. In two separate studies of prodromal symptoms (11, 12), Paykel's Clinical Interview for Depression (13), a modified, expanded, and more sensitive version of the Hamilton Rating Scale for Depression (14), was chosen. Healthy control subjects, matched for sociodemographic variables, were also interviewed in order to exclude the possibility that a high rate of symptoms was also reported in a normal population.

Measurement need not limit itself to psychometric tools. The past decade has witnessed an upsurge of research on biological markers in affective disorders, and the joint use of biological and psychometric tools may be feasible. This, however, would require prospective studies; it would allow the exploration of biological correlates of the prodromal as well as of the acute phase of the clinical syndrome.

### *Assessment Strategies*

The detection of affective prodromes may be retrospective as well as prospective. In this sense, there are several similarities with the methodological problems of research of life events (15). Retrospective studies have obvious inherent risks, in particular, biased or distorted recall. The more distant the period of recall, the more likely the life change is to be underestimated and the accuracy of recall to be inversely proportional to the remoteness of the time period to be recalled (16). If the patient or relatives are questioned about events during a crisis, they are likely to distort the meaning and seriousness of the events (17). Anxious patients receiving an active drug were found to be more likely to report positive events and less likely to report negative events than were patients receiving placebo (18). In life events research, a delay in the interview until the acute disturbance has passed (19, 20) results in a less distorted history.

The study on prodromal symptoms of schizophrenia by Herz and Melville (3) in 1980 provided seminal methodologic insights in this direction. They developed and validated the Early Signs Questionnaire, a structured interview with a few open-ended questions based on a number of other symptom rating scales and clinical experience. The authors administered the interview to 145 chronic schizophrenic patients and 80 family members. Most patients and family informants were aware of a prodromal period during which the patients experienced such symptoms as difficulty sleeping or concentrating, loss of appetite, and feeling depressed (3). The administration of the Early Signs Questionnaire alerted the clinician and allowed early treatment that prevented the onset of a psychotic episode of the usual severity (6). However, only outpatients functioning at a stable level and inpatients who had recovered sufficiently were asked about prodromal symptoms of schizophrenia (3).

Herz's model for detecting prodromal symptoms of schizophrenia (21) largely pertains to chronic illnesses characterized by exacerbations and remissions and is thus not readily applicable to investigating unipolar depression or panic disorder. Its feasibility, however, was demonstrated by studies regarding the onset of panic attacks (11) and depressed mood (12) as the beginning of acute illness and the 6 months preceding them as the prodromal phase. Chronic illnesses such as schizophrenia also lend themselves to prospective studies of prodromal signs and symptoms (4, 5), in which, of course, problems of biased recall are less bothersome. Birchwood et al. (5) developed and implemented a monitoring system for early signs of schizophrenia in which they used patients and families as observers (and both self-rated and observer-rated methods). Early administration of medication may modify the progression of an illness, which introduces another methodological problem. For example, in a study of intermittent lithium medication for patients with bipolar disorder (22), the investigators may have erred on the side of safety, and lithium was administered at the first appearance of symptoms that might have been merely unimportant fluctuations of mood.

### *Overlaps With Other Phases of Illness*

There are three kinds of symptoms that may confound the study of prodromes. One involves premorbid traits (neurotic traits or traits of a personality disorder) that may become more prominent at times of stress. The state-trait dichotomy and its psychometric counterparts (9) are thus often situated on a continuum with blurred borders that do not permit clear-cut differentiation. A second area of overlap involves subclinical fluctuations in chronic affective conditions such as bipolar disorder. Patients with bipolar disorder who are clinically stable when treated with lithium display mood swings when followed up on a biweekly basis (23). Such subclinical fluctuations are unrelated to prodromes of a relapse. Finally, after an acute episode of affective illness, despite apparent recovery, residual symptoms may persist. Akiskal et al. (24) illustrated this phenomenon in unipolar depression. The symptoms that may be interpreted as prodromes of a depressive relapse may thus be residual from the previous episode or characterologic disturbances (24). A careful psychometric assessment before recovery may decrease this risk (12, 25).

## AFFECTIVE PRODROMES

### *Bipolar Disorder*

Kraepelin (26) described the prodromal phase of acute mania as follows: "The beginning of the illness is always very sudden; at most headaches, weariness, lack of pleasure in work or a great busyness, irritability, sleeplessness, precede by some days or weeks the outbreak of the more violent manifestations. . . . " Indeed, a rapid buildup of mania (typically in 1–7 days) was subsequently confirmed by studies of inpatients at the National Institute of Mental Health (27–29). Winokur (30) studied the onset of bipolar episodes, defined as the period of time that transpires between the development of symptoms and the point at which the patient enters a study at the time of hospital or clinic admission. He observed a significantly more rapid onset of mania than of bipolar or unipolar depression.

Other investigations have suggested a more rapid onset of bipolar depression than of unipolar episodes (31, 32). Molnar et al. (33) investigated the duration and symptoms of bipolar prodromes in 20 outpatients receiving lithium prophylaxis, who were clinically stable. Prodrome was defined as the interval from the time that the first symptom was recognized to the time when the symptoms reached maximum severity; it was investigated by means of a semistructured interview, whose reliability was cross-checked. The duration and symptoms of manic and depressive prodromes showed substantial variation among patients. Unlike previous studies (27–30), manic prodromes were found to be significantly longer than the depressive prodromes. The most frequently reported depressive symptoms were depressed mood, loss of energy, and difficulty concentrating. As for manic episodes, it was striking that all patients reported increased activity as a prodromal symptom.Elevated mood and decreased need for sleep were also common. Within each patient, there was a striking consistency in the prodromal symptoms that preceded each episode; that is, affective episodes in individual patients tended to begin according to consistent sequences. Relatives confirmed these sequences (33). The study of Molnar et al. (33) lends support to Court's remarks (34) on the fact that patients with bipolar illness, despite their characteristic lack of insight, often are able to recognize prodromal symptoms.

### *Unipolar Depression*

Hays (31) examined prodromal symptoms in 81 patients with endogenous depression. Four symptom patterns emerged: 1) sudden-onset depressions (associated with melancholic features and bipolar disorder); 2) gradual-onset depressions, in which mood disorder took months to develop and was related to common stressful life events; 3) neurotic-onset depressions, commonly preceded by anxiety disorders; and 4) "fluctuating onset" depressions, in which symptoms displayed considerable fluctuations in severity before reaching full force. Hopkinson (35) interviewed 43 inpatients suffering from "depressive psychosis." About 30% showed a prodromal phase characterized more by "tension and vague feelings of anxiety," than by other symptoms such as indecision and impaired concentration. Other studies have dealt with the rapidity of onset of depressive symptoms. Winokur (30) found, in a sample of 216 patients, that patients with depression spectrum disease (i.e., patients who had first-degree relatives with alcoholism), were much less likely to have an acute or abrupt onset than were other depressive patients. Young and Grabler (32) reported that in 11 depressed patients a rapid onset of symptoms was associated with the endogenous subtype, the absence of past or current nonaffective disorders, older age, and fewer stressful life events.

Fava et al. (12) investigated prodromal symptoms in the 6 months before the onset of depressed mood in 15 outpatients in their first episode of primary major depressive disorder. A semistructured interview based on Paykel's Clinical Interview for Depression (13) was performed 2 to 3 months after the initial evaluations, when the patients' symptoms had improved. Family members who had observed the patients were asked to provide additional information. Each of the 15 patients reported having at least one prodromal symptom before the onset of depressed mood. Generalized anxiety was present in 13 cases and irritability in nine. Other common symptoms were impaired work and initiative, fatigue, and initial and delayed insomnia.

These results support a description in the textbook by Mayer-Gross et al. (36, pp. 207–208): "The history of change in the patient's behaviour is characteristic and important; he retires from usual social activities, avoids his friends in the street, and, if forced into company, seems bored and inattentive and takes little interest in topics that usually elicit an active response . . . . An initial mood of indifference in depressive states may last for a considerable time, but sooner or later is replaced by the one of *sadness.*"

During a 6-month follow-up, after discontinuation of antidepressant drugs, four of the 15 patients relapsed and required further antidepressant drug treatment (12). In all cases, prodromal symptoms of relapse closely resembled those of the first episode, a phenomenon that was previously observed in bipolar disorder (33). The consistency of symptoms over time in each individual is not limited to prodromes but also applies to the affective episode. Paykel et al. (25) found some similarities in symptom patterns of 33 depressed patients between initial ratings at the height of a depressive illness and subsequent relapse several months later, after intervening recovery.

### *Biological Markers*

There is an impressive body of research on biological markers of depressive illness. The evidence suggests that abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis in depression (resistance to dexamethasone suppression, spontaneous plasma cortisol secretion, abnormal metyrapone responses, ß-endorphin and ß-lipotropin secretion, and corticotropin-releasing factor [CRF] challenge) tend to subside upon clinical recovery (37). In particular, abnormal dexamethasone suppression test (DST) results tend to normalize upon antidepressant treatment; failure to do so is often associated with a poor prognosis, indicating that full recovery from depression should include normalization of the HPA axis (38–44). As a result, persistent nonsuppression, despite antidepressant treatment, or reversion to abnormal DST results, may be prodromal signs of relapse in unipolar depression.

### *Panic Disorder*

Prodromal symptoms in panic disorder have been studied, particularly in agoraphobia. There are several published studies, and the results are conflicting. There is still disagreement among authors on the prodromal phase and early course of the disorder. According to Klein (45), phobic avoidance in panic disorder with agoraphobia is secondary to the panic attacks. Klein observed that when patients are suddenly struck by the first panic attacks, they develop persistent anticipatory anxiety and hypochondriacal fears. These lead to avoidant behavior, so that agoraphobia ensues. Several studies support Klein's view. Garvey and Tuason (46) noted that the agoraphobic symptoms had not preceded the panic attacks in any of the 12 patients experiencing both agoraphobia and panic attacks. Thyer and Himle (47) administered a questionnaire to 28 members of an agoraphobia self-help group. Twenty-two patients (79%) endorsed the statement, "My panics caused my agoraphobia," and the onset of panic attacks had preceded the development of agoraphobic avoidance by an average of 9 years. In the same vein, Uhde et al. (48) observed that 31 of 32 patients with agoraphobia had developed phobic avoidance behavior after the onset of panic attacks. Pathological degrees of generalized anxiety had become manifest after, rather than before, the onset of panic episodes. These results were confirmed by a study of 55 patients suffering from panic attacks (49) and by an investigation on the longitudinal course of panic disorder in 46 patients (50). All of these studies point to the lack of prodromal symptoms in panic disorder, which is unlike the longitudinal course of other affective (anxiety and depressive) disturbances (51).

Authors of some recent studies have described prodromal symptoms and have observed different sequences of events. Garvey et al. (52) found that 28% of 32 panic disorder patients had prodromal symptoms of generalized anxiety that lasted a median of 5 years before the occurrence of the first panic attack. Fava et al. (11) found that of 20 patients suffering from panic disorder with agoraphobia, 18 reported experiencing agoraphobic avoidance, generalized anxiety, and hypochondriacal fears and beliefs before the first panic attack. As in the case of patients with unipolar depression (12), after improvement the patients were assessed with Paykel's Clinical Interview for Depression (13). These findings were replicated in patients with panic disorder that occurred in the setting of neurocirculatory asthenia (53) and hypochondriasis (54). Lelliott et al. (55) found that 70% of 57 patients with panic disorder with agoraphobia had prodromal depression, anxiety, or avoidance. Agoraphobic avoidance preceded the first panic attack in 23% of the patients. These studies confirm Roth's observation that even though the first attack of panic often develops abruptly, "more detailed investigation will usually reveal that the disorder has not emerged out of an entirely clear sky and that the complex repertoire of avoidance behaviours and helpless dependence on others were not entirely without premorbid antecedents" (56, p. 36).

## CLINICAL AND RESEARCH IMPLICATIONS

Compared to research on the phenomenology of the clinical manifestations of the fully developed clinical syndromes, there is a dearth of studies on prodromal symptoms in affective disorders. However, the reports summarized in this article address important clinical issues that deserve further study.

### *Bipolar Disorder*

Lithium has emerged unquestionably as the treatment of choice for prophylaxis of bipolar disorder (57). Data on the optimal duration of lithium maintenance in bipolar disorder are lacking, and, consequently, few guidelines exist to help clinicians estimate the risks and benefits of terminating such treatment once the patient is clinically stable (58). The recommendation of indefinite, lifelong treatment has been successfully challenged in medical illnesses such as essential hypertension and in psychiatric disorders such as schizophrenia (21). Some authors advocate that this recommendation should be reconsidered also in bipolar illness (22). Relapse after the patient's discontinuation of lithium is well documented (59), yet little is known about the results of physician-selected lithium discontinuation (22). The prospect of indefinite treatment probably contributes to the high rate of noncompliance found among patients receiving lithium prophylaxis. Further, because of the high proportion of patients who fail to respond to lithium alone (57), supplementary medications may be required.

Since the appearance of prodromal symptoms may precede the full syndrome by weeks or months, if patients and their family members are educated to recognize the patients' characteristic prodromal symptoms, recurrences of affective disorder could be treated earlier and perhaps more effectively (33). In a first episode, it seems unlikely that either the patient or the relative could recognize the prodromal phase unless it strikingly differed from the patient's usual mood and appeared to be ominous. In the early 1960s, Jacobson (60) described a program for the early detection and control of hypomanic episodes, based on appraisal of individual prodromal symptoms and intermittent use of lithium. It is unknown in what proportion of patients there is an abrupt onset of changes in mood and, conversely, what proportion of stable bipolar patients display substantial clinical fluctuations, how many of these are innocuous, and how many end, in a crescendo, in a full affective episode.

Only a few studies have dealt with the psychological state of recovered bipolar patients. Studies using the MMPI (61), the BPRS (62), and the Middlesex Hospital Questionnaire (63) failed to detect significant differences between remitted bipolar patients and normal control subjects. However, studies employing the Symptom Questionnaire (SQ) (64) or the BPRS and the Symptom Questionnaire in a longitudinal design (23) revealed psychopathology in a substantial proportion of patients who were judged to be in remission. Such observation would also be relevant to models of bipolar illness (34, 57). In other words, there are inadequate data that help distinguish between residual symptoms and prodromal symptoms.

### *Unipolar Depression*

Several authors have studied recurrences in depressed patients (65, 66). Strategies involving pharmacological prevention of recurrences (58) as well as psychotherapy (57, 65) attempt to prolong the survival time of patients after discontinuation of antidepressants or reduction of dose. As in bipolar illness, early recognition of prodromal symptoms could be valuable. Kupfer et al. (67) outlined the clinical advantages of early treatment intervention in recurrent depression. Early treatment might shorten the episode, prevent suffering, and require lower doses of medication than treatment of the advanced stage of the disorder. Residual symptoms after treatment (68) have been correlated with poor long-term outcome. To our knowledge, there are no studies that have examined the relationship between prodromal and residual symptoms in unipolar depression. In one study anxiety and irritable mood were found to be prodromal symptoms (12). Both improved with drug treatment (69, 70); a sensitive self-rating scale detected significant differences between apparently successfully treated depressed patients and normal control subjects in anxiety (69) but not in hostility and irritable mood (70). Some residual symptoms may progress to become prodromal symptoms of relapse. We are currently exploring whether cognitive treatment directed toward residual symptoms after successful drug treatment of depression will yield long-term benefits. Both in bipolar (33) and unipolar (12) depression, prodromal symptoms were found to have large interindividual variability (between individuals with the same illness and between different illnesses), yet small intraindividual variation.

The last decade has shown a large interindividual variability also in biological correlates of depression, such as the DST (37). Through different depressive episodes (71) and within the same episode (72), however, results on the DST remain comparable for any single patient. DST results might be a prodromal sign in patients in whom the previous response is known. The study of biological markers in the prodromal, instead of the acute, phase of illness may shed some light on neuroendocrine mechanisms. For instance, Gold et al.'s theory (73) on combined CRF overdrive and adrenal hypertrophy would require increased basal ACTH levels early in the illness (74).

### *Panic Disorder*

Theoretically, the lack of prodromal symptoms would imply that the control of panic attacks, if necessary by drug treatment, would be essential in order to diminish avoidant behavior (75). Conversely, the presence of prodromal symptoms such as avoidant behavior would imply that patients should be exposed to the phobic situation, be desensitized, and reduce avoidant behavior: this may lead to a gradual reduction of panic attacks, thus avoiding relapse upon drug discontinuation (76). Residual symptoms in patients who recovered from panic disorder have been described (77, 78). In view of the conflicting results, it will require more studies before the cause of the evolution of agoraphobia with panic attacks can be determined. The current data suggest that in a substantial proportion of patients, psychopathology such as generalized anxiety or agoraphobic avoidance precedes the first attack of panic. In others, apparently the first panic attack can occur without conspicuous prodromal symptoms, and generalized (anticipatory) anxiety and phobic avoidance can develop subsequently.

In agoraphobia, the same problem exists as in other affective disorders. It is difficult to distinguish between residual and prodromal symptoms. The sequence of events that precede agoraphobia with panic attacks is of theoretical interest. The choice of treatments, however, will be determined by the effects of different methods compared in controlled trials (such as exposure and drug treatment of panic attacks).

## VULNERABILITY AND THE LONGITUDINAL STUDY OF AFFECTIVE DISORDERS

Weiner (79) has remarked that traditional, linear, restrictive, and oversimplified medical models in psychiatry should be supplanted by an updated multifactorial model based on modern biology of viral disease, taking into account predisposition to disease, the time and manner of infection, multiple disease forms, variable adaptive responses, and the role of social and cultural factors. However, for the study of psychiatric disorders, even this complex model of viral disease is oversimplified. Carroll (80) has emphasized that the operational definitions of *DSM-III* give only a flat, two-dimensional view of the patient's illness because they ignore features that earlier clinicians placed much weight upon, such as family history, previous episodes, and responses to previous treatments. The study of infectious disease, in its symptomatic subdivision among prodromal, acute, subacute, and residual phases, provides at least a warning against undue restrictions of explorations of the dynamic assessment of the patient, which includes biography. The longitudinal study of psychiatric disorders has been emphasized by psychoanalytic writers but also has a long phenomenological tradition. For example, Slater and Slater (81) in 1944 developed a heuristic theory of neurosis, based largely on phenomenological observations such as in soldiers under stress (82), whereby the neurotic constitution is predominantly determined by a large number of genes of small effect. The neurotically predisposed man is an individual who has a more than average susceptibility to environmental stresses of one or more kinds (81).

Several current research trends seem to move along similar lines. Cloninger (83) proposed a general theory of heritable personality traits and their neurobiological basis, underlying the development of anxiety states. Roth outlined a comprehensive model in which "agoraphobia develops as a long period of historical development in the course of which a faulty seam has been introduced in the failure of the personality" (84, p. 154). He stated that one aspect of the contribution of psychoanalysis has proved of lasting importance: "looking before and after" into the lives of patients. The temporal instability, variability, and the coexistence of syndromes; and the relationship of personality traits to symptoms of anxiety, panic, depression, hypochondriasis, and phobias (85–87) seem, indeed, to require a longitudinal, comprehensive point of observation. Such an approach may include consideration of the "stressful circumstances that have surrounded the onset of illness, the premorbid personality and its Achilles heels, the historical record of the patient's development, adjustment in childhood, the relationship with parents, sexual life within and out of marriage, his achievements and ambitions, his interpersonal relationships, his adaptation in various roles and the strength or brittleness of his self-esteem" (84, p. 154).

## CONCLUSIONS

Most of the studies on prodromal symptoms of affective disorders were carried out in the 1960s and are thus hindered by the methodological limitations that psychometrics entailed then. There is a need for new studies that use both retrospective and prospective designs. Retrospective studies may benefit from the insights of life events research and should employ observer-rated instruments based on the patient's history and that of relatives or friends, since such instruments may facilitate temporal organization of personal facts (88). Prospective designs may employ both observer- and self-rating instruments, since their combined use may increase sensitivity (9, 69), which is a crucial factor in measurement of prodromal symptoms. Appraisal of prodromal symptoms may lead to an improved conceptualization of affective disorders and, at least in some patients, may result in earlier treatment.

Physicians, in fact, may carefully collect data on prodromal symptoms of the acute episodes of illness of their patients. Such appraisal is best performed upon recovery of patients. Before discontinuing or decreasing medication or discharging the patient from treatment (including psychotherapy), physicians may educate patients and their families to be particularly aware of the specific symptoms that preceded the illness episode and to notify the psychiatrist if these occur again, so that medication or psychotherapy can be reinstituted. It should be noted that at times, the same symptoms as in the prodromal phase of the acute affective disorder may occur and not be followed by another episode.

The clinical decision about starting treatment again may be a difficult one. When in doubt, it is always possible to reassess the patient in a short time (e.g., 1 week) and to monitor the course of symptoms. In unipolar depression, when abnormal DST results were present in the illness episode, a new DST may be considered, and this may supplement phenomenological observation. In our clinical experience, certain symptoms disappear shortly after the patient sees the psychiatrist again, probably because of a nonspecific effect (reassurance).

Further research may help to develop specific guidelines for follow-up of patients who recovered from affective disorders.

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# Review of Bulimia Nervosa in Males

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*Objective: The authors describe the distribution of bulimia nervosa among males and identify characteristics that distinguish male bulimics from their female counterparts. Method: Potential references were identified through an English-language literature search using MEDLINE (1966 to April 1990) and through extensive manual searching of textbooks and reviews. All published works with original data or hypotheses concerning bulimia in males were included. Results: Bulimia affects approximately 0.2% of adolescent boys and young adult men, and males account for 10%–15% of all bulimic subjects identified in community-based studies. Compared to their female counterparts, male bulimics appear to have a later age of onset; higher prevalences of premorbid obesity, homosexuality, and asexuality; and less concern with strict weight control. These findings are discussed from biological, psychological, and cultural perspectives to develop a fuller understanding of the pathogenesis of bulimia in males. Conclusions: Bulimia in males has received relatively little attention in the literature. Future research should focus on more rigorous analytic studies that include matched comparison groups of female bulimic and male nonbulimic subjects. Such studies would not only benefit male bulimics but might provide insight into the nature of bulimia in both sexes.*

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Bulimia nervosa is characterized by recurrent episodes of binge eating combined with persistent efforts to prevent weight gain through purging, fasting, or vigorous exercise. In contrast to the *DSM-III* diagnostic criteria, which did not specify a minimum frequency of binge eating, the *DSM-III-R* criteria require at least two episodes of binge eating per week for at least 3 months. Prevalence estimates for bulimia have varied widely because of such differences in diagnostic criteria, as well as other differences in study design. Nevertheless, a recent review (1) suggests that the disorder affects approximately 1% of all adolescent girls and young adult women. Thus, bulimia is the cause of substantial psychiatric morbidity in the United States.

In recent years, there has been increased awareness that bulimia occurs in males, as well as females. Nonetheless, research and theoretical discussions concerning this subgroup remain scarce. In this review we highlight the methodologic problems of research on bulimia in males and then evaluate all available information on bulimia in males in order to 1) describe its distribution in the community and 2) identify characteristics that distinguish male bulimics from their female counterparts. The identification of such characteristics would improve diagnosis and treatment of bulimia in males and might increase our understanding of processes that are specific to bulimia in both sexes.

## METHODOLOGIC ISSUES

The pitfalls of epidemiologic research on bulimia are well known (1–3). They include potential problems with case definition, methods of case detection, response rates, and the generalizability of data predominantly from college students; many of these issues will be addressed in this review. The methodologic problems of research on bulimia in special subgroups, such as males, may be less apparent and will be discussed briefly.

Almost all studies of bulimia in males have relied to some extent on self-report questionnaires, yet rarely have investigators evaluated the performance of these instruments in male subjects. It cannot be assumed that the validity, reliability, and predictive value of these questionnaires are the same for both sexes. For example, women have been shown to be more likely than men to label eating large amounts of food as a "binge" (4). Furthermore, one might expect male-female differences in the self-reporting of binge eating given that it

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is more socially sanctioned for males than for females (4, 5). Ultimately, these sex differences may lead to differential detection of bulimia itself. In fact, one study of five male bulimic subjects (6) found that a screening instrument which had been validated among female subjects, and was thought to be quite sensitive, would not have identified any of these male patients as suffering from an eating disorder. The ultimate effects of differential instrument performance are unknown, but this issue is clearly an important potential limitation to research on bulimia in males, especially that concerned with the detection of sex differences.

Studies of the "typical" male bulimic that have been reported to date are based almost entirely on small case series at the authors' institutions. Not only does a small number of subjects affect both the validity and the strength of inferences drawn from a study, but when these study groups are smaller than predicted by community-based prevalence data, they suggest that clinic-based subjects may not be representative of all bulimics. It is clear from the literature on bulimia among females that only a small subgroup of those with bulimia are actually in treatment and that this group tends to have a more severe form of bulimia (1). The possibility of sampling bias in clinic-based studies has particular relevance to research on bulimia among males for at least two reasons. First, many clinicians are unaccustomed to the idea of bulimia in males (7, 8) and, as a result, they may tend to identify only the most severe cases among males. Second, many bulimic males may be embarrassed about seeking treatment for a stereotypically feminine disorder (9, 10), a situation that could bias study groups toward males who feel more comfortable with the feminine role or who differ from the average bulimic male on other dimensions. We will examine the possibility of a sampling bias by comparing the proportion of male bulimics in community-based studies with the proportion in clinic-based case series; a discrepancy would suggest that clinically identified subjects may not be representative of all male bulimics. Even if the data support this possibility, however, subsequent analysis of the "typical" male bulimic patient would still provide clinically useful information as it is these patients who are under psychiatric care. Furthermore, any identified sex differences among clinic-based patients might still reflect actual differences between male and female bulimics in the community.

Finally, studies of bulimia in males present the opportunity to identify 1) sex differences in the clinical presentation, treatment, and prognosis of bulimia and 2) etiologic factors that either are unique to male bulimics or are essential to bulimia in both sexes. The latter objective requires not only a comparison of male and female bulimics but also a comparison of bulimic and nonbulimic males, coupled with a detailed understanding of bulimia in females. Unfortunately, no study to date has compared bulimic males with a suitably matched group of nonbulimic males. Furthermore, most analytic studies have included inadequate comparison groups to achieve either objective. In many reports, a comparison group is simply lacking and undocumented impressions are used for comparison. More frequently, female bulimic subjects only are used as the comparison group, usually by means of data culled from the bulimia literature; probable differences in data collection alone diminish confidence in these studies' conclusions. Relatively few studies of bulimia in males incorporated a comparison group of female bulimic subjects who were seen in the same institution and to whom identical diagnostic criteria were applied (10–14).

## METHOD

Potential references were identified through a search of the English-language literature using MEDLINE (1966 to April 1990) and through examining the reference lists in the identified works. The literature search was supplemented by extensive manual searching of articles, textbooks, and monographs on eating disorders and on male studies. All published works with original data or hypotheses concerning bulimia in males were included.

## PREVALENCE AND INCIDENCE

Twenty-four studies reported community-based prevalence data on bulimia in males (15–38) and are presented chronologically in table 1. Six of these studies (15, 18, 20, 21, 27, 29) were excluded from further analysis of bulimia prevalence because of response rates less than 70% (15, 18, 21), fewer than 100 male subjects (20, 21, 27), or questionable case-finding procedures (29). The two studies in which the investigators attempted to interview all respondents were exempted from these exclusionary criteria because we felt their superior method of case detection may have counteracted the disadvantages of their low response rate (30) and small number of male subjects (23).

To address differences in diagnostic criteria and method of case detection, differences which have led to wide variation in prevalence estimates for females (1), the studies of bulimia prevalence in males were analyzed along both dimensions. Six studies relied on *DSM-III* (17, 23, 25, 32, 36, 37), six on modified *DSM-III* criteria with a specified minimum frequency of binge eating (16, 19, 22, 24, 26, 31), and five on either Russell's criteria or *DSM-III-R* (28, 30, 34, 35, 38). Among the studies using the *DSM-III* criteria, the mean prevalence of bulimia in male subjects was 1.1% (range, 0.0%–4.3%); for those using modified *DSM-III* criteria, the mean was 0.5% (range, 0.0%–1.2%); and among the five studies using the most stringent criteria, the mean was 0.2% (range, 0.1%–0.5%). As expected, the mean prevalence estimates declined as stricter diagnostic criteria were used.

The prevalence studies were also classified according

**TABLE 1. Studies of the Prevalence of Bulimia Nervosa in Males**

| | Subjects | | | | Method | | Prevalence (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Sex | | | | | | | |
| Reference | Type[a] | F | M | Response (%) | Case-Finding Procedure[b] | Diagnostic Criteria | F | M | Ratio |
| Halmi et al., 1981 (15) | New York state, summer students at suburban college campus, mean age=26 | 359 | 180 | 66 | Questionnaire (BEQ) | Partial *DSM-III* (binging frequency not reported) | 19.0 | 5.0 | 3.8 |
| Pyle et al., 1983 (16) | Midwestern college freshmen | 575 | 780 | 98 | Questionnaire[c] | Modified *DSM-III* (≥1 binge/week) | 4.5 | 0.4 | 11.3 |
| Pope et al., 1984 (17) | High school students | 155 | 107 | 86[d] | Questionnaire[e] | *DSM-III* | 6.5 | 0.0 | — |
| | College students | 102 | 47 | 46[d] | Questionnaire[e] | *DSM-III* | 18.6 | 0.0 | — |
| Gray and Ford, 1985 (18) | College students | 220 | 119 | 54 | Questionnaire | *DSM-III* | 13.0 | 4.2[f] | 3.1 |
| Healy et al., 1985 (19) | Dublin, Ireland, college students | 701 | 361 | >95 | Questionnaire | Modified *DSM-III* (≥1 binge/week+ awareness of abnormal eating) | 2.7 | 0.0 | — |
| Maceyko and Nagelberg, 1985 (20) | Georgia, high school students | 168 | 89 | — | Questionnaire | Modified *DSM-III* (≥1 binge/week) | 4.7 | 0.0 | — |
| Edwards and Nagelberg, 1986 (21) | Georgia, college students | 51 | 27 | 38 | Questionnaire (modified BS) | *DSM-III* | 14.0 | 19.0 | 0.7 |
| Pyle et al., 1986 (22) | Midwestern college freshmen | 722 | 660 | 96 | Questionnaire | Modified *DSM-III* (≥1 binge/week) | 3.5 | 0.0 | — |
| Rand and Kuldau, 1986 (23) | Florida, community volunteers aged 16–35 | 144 | 88 | — | Interview | *DSM-III* | 0.7 | 0.0 | — |
| Zuckerman et al., 1986 (24) | New England, college freshmen and seniors | 631 | 276 | 69[d] | Questionnaire (modified EDI) | Modified *DSM-III* (≥2 binges/week) | 4.0 | 0.4 | 10.0 |
| Gray et al., 1987 (25) | Black college students | 341 | 166 | ~100 | Questionnaire | *DSM-III* | 3.0 | 2.0 | 1.5 |
| Greenfield et al., 1987 (26) | New England prep school students | 337 | 424 | 78[d] | Questionnaire (modified BEQ) | Modified *DSM-III* (≥1 binge/week) | 4.0 | 0.8 | 5.0 |
| Lakin and McClelland, 1987 (27) | Midwestern high school students | 71 | 55 | 70 | Questionnaire (BS) | Modified *DSM-III* (≥1 binge/week) | 3.2 | 0.0 | — |
| Schotte and Stunkard, 1987 (28) | College students | 994 | 942 | 97 | Questionnaire, interview | *DSM-III-R*; prevalence adjusted for 22% false positive rate of questionnaire | 0.7 | 0.1 | 7.0 |
| Cullberg and Engström-Lindberg, 1988 (29) | Sweden, suburban catchment area, aged 16–24 | 4,651 | 4,762 | — | Survey of health care workers | *DSM-III*; 2-year prevalence | 0.47 | 0.02 | 23.5 |
| Drewnowski et al., 1988 (30) | College students, national probability sample | 507 | 500 | 56 | Telephone interview | Modified *DSM-III-R* (required current dieting or desire for weight loss) | 1.0 | 0.2 | 5.0 |
| Gross and Rosen, 1988 (31) | Northeast high school students | 677 | 653 | 90 | Questionnaires (EAT, EDI) | Modified *DSM-III* (≥1 binge/week) | 9.6 | 1.2 | 8.0 |
| Lachenmeyer and Muni-Brander, 1988 (32) | High school students | 642 | 619 | — | Questionnaires (EAT-26, BEQ) | *DSM-III* | 8.7 | 4.3 | 2.0 |
| Whitehouse and Button, 1988 (33) | England, technical college students | 446 | 132 | 99 | Screening questionnaire (EAT), interview | *DSM-III* and Russell's criteria (44); EAT score >32 | 1.6 | 0.0 | — |
| King, 1989 (34) | London, general practice patients aged 16–35 | 534 | 186 | 96 | Screening questionnaire (EAT), interview | Russell's criteria; EAT score >19 | 1.1 | 0.5 | 2.2 |

**TABLE 1 (continued)**

| | Subjects | | | | Method | | Prevalence (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Sex | | | | | | | |
| Reference | Type[a] | F | M | Response (%) | Case-Finding Procedure[b] | Diagnostic Criteria | F | M | Ratio |
| Striegel-Moore et al., 1989 (35) | Yale University freshmen | 450 | 590 | 74[d] | Questionnaire | Modified *DSM-III-R* (≥3 binges/week) | 3.8 | 0.2 | 19.0 |
| Wells et al., 1989 (36) | Christchurch, New Zealand, probability sample aged 18–64 | 994 | 564 | 70 | Interview (DIS) | *DSM-III* | 1.9 | 0.2 | 9.5 |
| Whitaker et al., 1989 (37) | New York state, semirural high school students | 2,544 | 2,564 | 91 | Questionnaires (original, EAT) | *DSM-III* | 1.2 | 0.4 | 3.0 |
| Timmerman et al., 1990 (38) | Midwestern high school students | 686 | 705 | 99 | Questionnaire | *DSM-III-R* | 2.0 | 0.1 | 20.0 |

[a] Study conducted in United States unless otherwise indicated.

[b] BEQ=Binge Eating Questionnaire (15), BS=Binge Scale (39), EDI=Eating Disorders Inventory (40), EAT=Eating Attitudes Test (41), EAT-26=Eating Attitudes Test-26 (42), DIS=Diagnostic Interview Schedule (43).

[c] 100% sensitivity in bulimic subjects.

[d] Males.

[e] 90% sensitivity in bulimic subjects.

[f] Additional 4% of men classified as "near bulimic."

to method of case detection. The majority of studies (12 of 18) relied exclusively on self-report questionnaires (16, 17, 19, 22, 24–26, 31, 32, 35, 37, 38), and only one study (33) incorporated a simple two-stage design: a screening questionnaire and subsequent interview of potential bulimic subjects to establish a definite diagnosis. The five remaining studies were either two-stage studies that included evaluation of the screening instruments or single-stage studies in which all subjects were interviewed (23, 28, 30, 34, 36). Among the studies using questionnaire data alone, the mean prevalence of bulimia in male subjects was 0.8% (range, 0.0%–4.3%); in the single study using a simple two-stage design, the prevalence was 0.0%; and among the five studies using the more sophisticated interview-based design, the mean prevalence was 0.2% (range, 0.0%–0.5%). These findings are consistent with those obtained when the studies were grouped by diagnostic criteria (already discussed) and when the studies were grouped according to student versus nonstudent samples (data not shown) (23, 34, 36). Taken together, the data suggest that bulimia affects approximately 0.2% of all adolescent boys and young adult men. The female-to-male prevalence ratios are also reported in table 1, and they confirm the well-known female predominance in bulimia (1–3). The ratios range from 1.5 to 20.0 and cluster around 5–10 (24, 26, 28, 31, 36). These results indicate that males make up approximately 10%–15% of bulimic persons in the community. This proportion is larger than that typically found in clinic-based case series (14, 44–49), in which the prevalence for males ranges from 1% (49) to 11% (48) and has an overall mean of 6%. This discrepancy supports our speculation that male bulimics are less likely to seek treatment than their female counterparts.

Although it is unclear what isolated bulimic behaviors mean in terms of bulimia risk, most investigators, but not all (50), believe that there is a continuum of "bulimic behaviors and attitudes" and that bulimia represents the pathological endpoint of that spectrum (51). We share this belief and consequently have reviewed all 29 studies reporting community-based prevalence data on specific bulimic behaviors in males (4, 5, 15, 16, 18–28, 30, 32, 35, 37–39, 52–59). Estimates of the prevalence of binge eating vary widely and, to a large extent, reflect how the investigators defined the term for their respondents and whether they specified a minimum frequency of binge eating. Twenty of the 27 studies of binge eating did not stipulate a minimum frequency (4, 5, 15, 16, 18, 19, 21–23, 25–27, 32, 35, 37, 39, 53, 54, 57, 58); among these, the prevalence varied from 5% to 80% and there was no clustering. Among the seven studies that specified a minimum frequency of at least biweekly (28) or weekly (20, 24, 30, 38, 52, 59) binge eating, the reported prevalences ranged from 1% to 40% and the majority clustered in the 10%–20% range. The female-to-male prevalence ratios for binge eating varied from 0.2 to 2.8 and clustered in the 1.5–2.0 range. Although female-male comparisons are fraught with difficulty because of probable sex-specific differences in both the definition of "binge eating" (4) and its societal acceptance (4, 5), it appears that the rate of binge eating among males may be almost comparable to that among females.

Estimates of the prevalence of self-induced vomiting among males were presented in 16 studies (5, 15, 18, 23–26, 28, 32, 37, 39, 52, 54–57). The reported prevalences ranged from 0% to 8%; there was one report of 23% (32), yet most of the studies clustered around 1%–3%. The female-to-male prevalence ratios for self-induced vomiting ranged from 0.9 to 9.7, and the majority clustered around 4–5, midway between the sex ratios for binge eating and bulimia. These results may reflect the fact that men react to binge eating with less dysphoria (5, 16, 37, 39, 58) and thereby are at lower risk for guilt-induced purging.

Only two studies have focused on the incidence of bulimia in males. Cullberg and Engström-Lindberg (29) sought all cases of eating disorders in a Swedish suburb by sending letters to mental health practitioners and general internists in the area. Among approximately 4,700 males aged 16–24 years, they found a 2-year bulimia incidence of 0.0%. It is unclear how effective their case-finding procedure was, however, since their reported bulimia prevalence rates in both males (0.02%) and females (0.47%) were well below any other prevalence estimates in the literature (60). Striegel-Moore et al. (35) reported a 1-year bulimia incidence of 0.8% in female college students and 0.2% in male college students. Although the number of men in their study was substantial (N=590), given the relatively low prevalence of bulimia and the long duration of this disorder, it probably was not large enough to generate reliable incidence figures.

## RISK FACTORS

As with most psychiatric disorders, a multifactorial process probably causes bulimia. As discussed earlier, investigators have neglected direct epidemiologic study of factors that increase (or decrease) a specific male's risk of bulimia. Instead, efforts have focused on identifying factors that distinguish male from female bulimics, differences that may prove clinically useful and may help to explain the marked sex difference in the prevalence of bulimia.

### *Age at Onset*

Males may develop bulimia later than females. Literature reviews have indicated that the average age at bulimia onset in females is between 15 and 18 years (60, 61). By contrast, the mean age at bulimia onset has ranged from 18 to 26 years in case series of five or more male patients (6, 10–12, 14, 47, 62). In all five studies that directly compared male and female subjects (10–12, 14, 29), the mean age at bulimia onset in the male subjects was higher than that in the female subjects, although this difference was described as statistically significant in only one report (12). In the remaining studies, the results of appropriate statistical analyses were not reported (14, 29) or the subject groups were so small that only extremely large age differences could have reached statistical significance (10, 11). Thus, these preliminary data suggest that males develop bulimia a few years later than females, but larger studies are needed to confirm this possibility.

### *Premorbid Weight*

Although American males and females do not differ in prevalence of obesity (63), male bulimics may have a higher prevalence of premorbid obesity than their female counterparts. In an anecdotal report, Robinson and Holden (62) found that all four of their male bulimic subjects without anorexia nervosa had been obese before developing bulimia. This impression was supported by Herzog et al. (11), who found that a history of obesity was significantly more prevalent among their male bulimic subjects (nine of 14, 64%) than among their female bulimic subjects (34 of 92, 37%) (Fisher's exact test, p=0.05). Schneider and Agras (10) compared 15 male bulimic subjects with a matched group of 15 bulimic female subjects, and they also found that the male subjects had been heavier than the female subjects before developing bulimia (129% of ideal body weight versus 111%, respectively) and were also relatively heavier at the time of diagnosis (110% versus 95%). Although neither difference reached statistical significance, the 95% confidence intervals for both the premorbid mean difference of 18% (−2.3, 32.3) and the pretreatment mean difference of 15% (−1.6, 37.6) are consistent with the results of Herzog et al. (11). Finally, Edwin and Andersen (13) studied 12 normal-weight male bulimic subjects and found that the average maximum premorbid weight was 155% of their ideal body weight, in contrast to a maximum of 121% in 13 matched female bulimic subjects ($p<0.005$). In sum, the current evidence suggests that prebulimic males tend to be more overweight than prebulimic females. Larger studies with adequate statistical power will be necessary before any firm conclusions about this sex difference can be drawn.

### *Body Image and Dieting*

In both male and female bulimics, dieting usually precedes binge eating and may in fact precipitate binge eating by a variety of physiological, cognitive, and emotional mechanisms (60, 62, 64, 65). The literature suggests that men are relatively protected from dieting as a risk factor for bulimia, possibly because of differences in the ways men and women view their bodies (66, 67). Survey research with both national probability samples (54) and college students (68–71) indicate that males, in general, are more satisfied with their bodies and perceive their bodies with less distortion than do females. For example, Salmons et al. (71) surveyed British secondary school students and found that the girls became progressively more dissatisfied with their body shapes and sizes as they aged from 11 to 18 years, whereas the boys were relatively unconcerned about their bodies. In the United States, Kaplan et al. (70) studied junior and senior high school students and found that girls were more likely than boys to overestimate their own weight. Furthermore, whereas girls tended to be depressed when overweight, boys were more likely to be depressed when underweight.

The more positive body image of males is reflected in their lower prevalence of dieting. Most studies comparing dieting behavior in males and females have focused on college students and have found that about one-half as many men diet as women; the prevalence estimates range from 10% to 40% in men and from 60% to 90% in women (56, 67, 68, 72). Women are more likely to cite cosmetic reasons for weight control, whereas men are more likely to cite athletic interests (37, 56). In marked contrast to female students, many male high school and college students actually wish to gain, rather than lose, weight. For example, Drewnowski and Yee (72) surveyed freshmen at a Midwestern university and found that whereas 85% of the women wanted to lose weight, the men were almost evenly split: 40% wanted to lose and 45% wanted to gain weight. Thus, to the extent that dieting acts as both a risk factor and a precipitant of bulimia, males are relatively protected from the disorder by their more positive body image and lower prevalence of dieting.

### *Occupations and Athletic Pursuits*

As with females (73), males who are in occupations or athletic pursuits that emphasize body weight may be at increased risk for bulimia. Gwirtsman et al. (64) reported two illustrative cases; one involved an 18-year-old whose bulimia was precipitated by his need to become a skinny rock musician, and the other involved a 23-year-old man who began dieting in order to develop a "hip" image within the fashion industry and developed bulimia 2 years later. Both Andersen (74) and Katz (75) reported male patients whose initiation of rigorous athletic regimens precipitated bulimia. Finally, King and Mezey (76) described several male jockeys who dropped out of training because of persistent weight loss, accompanied in one case by binge eating and self-induced vomiting. Although none of these case reports directly addressed the risk of bulimia, a few studies have shown that certain types of male athletes—such as body builders (77), wrestlers (78), and jockeys (76)—score higher than other males on the Eating Attitudes Test (41). Larger studies of the prevalence and incidence of bulimia among "high-risk" male occupational and athletic groups might verify the implications of these preliminary studies.

### *Sexuality*

There is persuasive evidence that male bulimics have a higher prevalence of homosexuality than their female counterparts and that homosexuality acts as a risk factor for bulimia in males. The estimated prevalence of homosexuality in the general population is higher among males (6%–10%) than among females (2%–4%) (79). Thus, to demonstrate that homosexuality is particularly associated with bulimia in males, the sex difference in the prevalence of homosexuality among bulimic subjects should exceed that expected from a comparison of males and females in the general population. Robinson and Holden (62), in an uncontrolled case series, found that three (33%) of their nine bulimic men were homosexual, a proportion that exceeds the prevalences expected in both bulimic women and nonbulimic men. Statistically significant differences were reported in three of the four studies that directly compared male and female subjects (10–12, 14). Schneider and Agras (10) found that homosexuality or bisexuality was significantly more prevalent among bulimic men (eight of 15, 53%) than among a matched comparison group of bulimic women (none of 15, 0%). Similarly, Woodside et al. (14) found that five (63%) of eight bulimic men were either homosexual or bisexual, as opposed to only four (1%) of 345 bulimic women seen in the same clinic. Herzog et al. (11) also reported significantly more homosexuality among 14 bulimic and 13 anorexic men (26%) than among 92 bulimic and 50 anorexic women (4%) seen in the same clinic; bulimia-specific analyses were not reported.

By contrast, Turnbull et al. (6) found no reported homosexuality in a case series of only five bulimic men. More important, Pope et al. (12) found that only one (7%) of 15 bulimic men reported homosexual activity; sexual preference data from their comparison group of bulimic women were not reported. The authors suggested that the low proportion of homosexuality may reflect the fact that their subjects were drawn from a suburban area, but Schneider and Agras (10) reported a high rate of homosexuality and bisexuality in their suburban sample. Alternatively, the lower prevalence of homosexuality found by Pope et al. could reflect the fact that the men in that study had a mean age at onset of 25.8 years and therefore may represent a male subset with a relatively late onset of bulimia; homosexual bulimic males may develop their illness closer to puberty, when sex role definition is a major issue. For example, all three of the homosexual bulimic men in the case series of Robinson and Holden (62) noted the onset of disordered eating behavior at age 15, and in two cases this was directly related to conflicts over homosexuality.

Three studies have approached the association between homosexuality and bulimia from the other direction; that is, they have begun with a group of homosexual men and have examined the prevalence of disordered eating behaviors and attitudes in this group. Silberstein et al. (80) compared 71 homosexual men with 71 heterosexual men and found that the homosexual men were more dissatisfied with their bodies and considered physical appearance to be more important to their sense of self than did the heterosexual men. Among the men who wanted to be thinner, only the homosexual men showed attitudes and behaviors associated with disordered eating, as measured by the Eating Attitudes Test (41). Yager et al. (81) compared 49 homosexual male college students with 300 other male students and found that a higher proportion of homosexual students reported past or present problems with binge eating, diuretic use, feeling terrified of being fat, and feeling fat despite other people's perceptions. In addition, the homosexual students scored higher than the comparison group on the overall Eating Disorders Inventory (40) and on the specific items regarding drive for thinness, bulimia, body dissatisfaction, ineffectiveness, and maturity fears. Herzog et al. (82) replicated the latter study in their comparison of 43 homosexual men and 32 heterosexual men. In addition to scoring higher on the "drive for thinness" scale of the Eating Disorders Inventory, these homosexual men showed less satisfaction with their body builds and were more likely to desire weights below their ideal weights. In summary, the preponderance of reported data suggest that homosexuality is associated with a higher than normal risk of bulimia in males; there is no evidence for a similar association in females (60).

In addition to homosexuality, bulimic males are frequently described as lacking sexual interest of any kind. To our knowledge, the prevalence data on asexuality are not available, but if asexuality is less common among males than females, as is commonly assumed (83), the asexuality of bulimic males should provoke particular interest. The earliest description of this phenomenon came from Russell's series of 30 bulimic patients, 28 women and two men (44); both men were described as having "extremely limited" sexual experience. Gwirtsman et al. (64) discussed the sexuality of two of their three male bulimic subjects; both patients had low libido (which may have been secondary to concurrent depression), and one also noted "anxieties about the possibility he might be homosexual." Pope et al. (12) found that four (27%) of 15 men were sexually inactive while bulimic but resumed sexual activity after treatment with antidepressants. In the only direct comparison of male and female subjects, Herzog et al. (11) found that lack of sexual relations was significantly more common among male patients with eating disorders than among female patients seen in the same clinic; bulimia-specific analyses were not reported. The proportion of asexual men in all of these studies suggests an association between asexuality and bulimia in males, an association that contrasts with the evidence that bulimic females are at least as sexually active as nonbulimic females (60).

Finally, several studies suggest a lower prevalence of marriage in bulimic men than in their female counterparts. Whereas approximately 30% of men aged 20–24 years in the general population are married (84), it has been reported that only 8%–13% of comparably aged bulimic men are married or divorced (10, 47, 62); these rates are also lower than the 30% marriage or divorce rate of bulimic women (60). Although the relatively low marriage rate of bulimic men may be partially explained by the fact that American men tend to marry later than women (84), Schneider and Agras (10) found that marriage or divorce was significantly less prevalent among bulimic men (two of 15, 13%) than among an age-matched comparison group of bulimic women (nine of 15, 60%). The lower marriage rate for bulimic men than for either bulimic women or nonbulimic men is consistent with the data on homosexuality and asexuality.

### *Drug and Alcohol Abuse*

Clinical investigators have reported higher than expected prevalences of drug and alcohol abuse among male bulimic patients (10, 47, 62), a finding consistent with the literature on bulimia in female patients (60). There is preliminary evidence that cocaine-abusing males are particularly likely to be bulimic; the evidence regarding alcohol abuse is more equivocal. Jonas et al. (85), in a study of 259 cocaine abusers, found that 21% of the men met the *DSM-III* criteria for bulimia, compared with 23% of the women. Thus, whereas the prevalence of bulimia among males in the general population is one-fifth to one-tenth the prevalence among females, among these cocaine abusers similar proportions of men and women were bulimic. It is premature to generalize these results to all male bulimics in the United States, yet the cross-sectional data are intriguing and if confirmed would give rise to three possibilities: cocaine abuse may disproportionately increase males' risk of bulimia, bulimia may disproportionately increase males' risk of cocaine abuse, or the association between bulimia and cocaine use may be mediated by a third factor. Prospective studies of cocaine abusers would be helpful in clarifying this issue.

Three other studies, focusing more on the relationship between alcohol use and bulimic behaviors, have produced contradictory results; one suggested a stronger association between substance abuse and bulimic behaviors in males than in females (86), and the other two suggested the reverse (16, 38). Claydon (86) studied college students whose parents were alcoholics; these students' rate of substance abuse was three to four times that of comparison subjects. The prevalence of a "possible eating disorder" (i.e., binge eating and "bulimia") was seven times as high among the male offspring as among the male comparison subjects, whereas the prevalence among the female offspring of alcoholics was only 1.5 times as high as that among their female counterparts. Although statistical tests of significance were not reported for these data, the differences suggest that being a child of an alcoholic parent particularly increases a male's risk of having an eating disorder.

By contrast, two large prevalence studies reported a stronger association between bulimic behaviors and substance abuse in females than in males. Timmerman et al. (38), reporting on a questionnaire-based study of high school students in the Midwest (705 boys, 686 girls), found a significant association between self-reported alcohol abuse and three or more *DSM-III-R* criteria for bulimia in both sexes; the association between alcohol abuse and four or more criteria for bulimia was significant in girls only. This reported sex difference, however, may have been due to statistical difficulties inherent in finding a significant association in the relatively small number of boys (N=33) versus the larger pool of girls (N=78) who fulfilled four or more *DSM-III-R* criteria. Leon et al. (5) found that a family history of substance abuse was reported by 43% of female binge eaters and 17% of female non-binge-eaters; among males, the proportion (26%) did not differ between binge eaters and non-binge-eaters. Clearly, whether substance abuse puts either sex at disproportionately higher risk for bulimia remains an unresolved question; further studies focusing on sex differences in the relationship between substance abuse and bulimia are needed to clarify the nature of this association.

### *Other Risk Factors*

Studies of bulimia in males have touched on several other risk factors, such as socioeconomic status, race, premorbid personality, and family pattern. With regard to socioeconomic status, only one study directly compared male and female bulimic subjects, and it found a slightly increased proportion of upper-class subjects in both groups (11). The series of nine male bulimic patients presented by Robinson and Holden (62) also had a somewhat higher than average proportion of upper-class subjects. Nonetheless, a recent prevalence study of Midwestern high school students indicated that high socioeconomic status was associated with bulimic behaviors in girls but not in boys (38).

Two studies that examined the relationship between race and bulimic behaviors in males (25, 87) suggested that both male and female blacks are less likely to perceive themselves as overweight, are more likely to be satisfied with their appearance if overweight, and have higher rates of binge eating than their white counterparts. Although these findings have led investigators to conclude that blacks of both sexes may be at lower risk for bulimia (25, 87), one report (88) suggested that the prevalence of the disorder among male and female blacks may be increasing.

With respect to premorbid personality, preliminary studies have reported social deviancy, impulsivity, and affective instability in male bulimic patients (10, 64, 89), which are consistent with the high rates among female bulimics (60). Similarly, the family patterns for bulimic subjects of both sexes have been described as unsupportive and chaotic (60, 62) and prone to secrecy (90). Unfortunately, no studies to date have specifically looked for sex differences in premorbid personality or family pattern or directly addressed either variable as a risk factor for bulimia in males.

## CLINICAL PRESENTATION

Frequently reported precipitants of bulimia in males include many of the risk factors already mentioned—e.g., being teased about being overweight (62, 74, 91), initiation of a physical development regimen for athletic pursuits (62, 64, 74), and anxieties about sexuality (62, 64, 74)—and interpersonal stressors, such as breaking up with a girlfriend (6, 62, 64, 74). It is not yet possible to address sex differences in the precipitants of bulimia because appropriate studies have not been reported.

The clinical features of bulimia are in most respects similar in both sexes, although there is some evidence that male bulimic subjects are less troubled by their binge eating and are less concerned with strict weight control than are their female counterparts. With regard to binge eating, Schneider and Agras (10) briefly noted that 15 male bulimic subjects, as compared to female bulimic subjects, ate more during a binge, were more likely to binge in public, and reported less guilt after binge eating in a public place (data not reported). Edwin and Andersen (13) performed psychometric testing on their group of bulimic men and women and found that the bulimic men were more satisfied with their bodies ($p<0.05$) and reported less discontent and more vigor ($p<0.0005$) than the bulimic women. In an anecdotal report, Lieberman (90) described a family with four bulimic children and stated that the two bulimic boys were less secretive about their symptoms or family confidences than their bulimic sisters. A much larger body of data comes from studies of binge eating among "normal" high school and college students (5, 16, 24, 37, 39, 58). These male students consistently reported less guilt and concern about binge eating than female students (5, 24, 37, 39) and had lower rates of depression or self-deprecation after binges (5, 16, 37, 39, 58, 92). Whether these differences also hold for male and female bulimia patients is less clear and must await further comparative studies.

With regard to weight control, Schneider and Agras (10) found that the mean desired body weight of male bulimic subjects (95% of ideal) was significantly higher than that of female subjects (85%), suggesting that the male bulimic subjects were more realistic about their ideal body weight. Edwin and Andersen (13) replicated these results in their comparison of 12 male and 13 female bulimic patients; the male subjects wished they weighed 106% of their ideal body weight on average, whereas the female subjects wanted to weigh 90% ($p<0.001$). In addition, male bulimics may rely less than female bulimics on laxatives, diuretics, and diet pills to lose weight (10, 47), and they may exhibit greater weight fluctuations over the course of their illness (10, 47). Finally, Killen et al. (55) found in a nonbulimic group of students that male subjects who purged were significantly heavier than those who did not purge, whereas this difference was not seen among the female subjects; these data suggest that the weight threshold for the initiation of purging may be higher for males than females and are consistent with the previously reviewed data showing that males in general are less concerned with their weight.

Male and female bulimics do not appear to differ with respect to frequency of binge eating or purging

(13, 47, 62) or frequency and severity of electrolyte or other medical disturbances (60, 93). With regard to the comorbidity of other psychiatric disorders, case series of male bulimic subjects have shown substantial rates of concurrent affective or anxiety disorders (12, 47, 62), personality disorders (particularly borderline and impulse control) (12, 64), and family histories of affective disorders (12, 47, 64). Nonetheless, it is not known whether male bulimics have a higher rate of concurrent psychiatric illness than their female counterparts. In the only direct comparison of male and female bulimic subjects along this dimension, Pope et al. (12) found that 67% (10 of 15) of their male bulimic subjects had either current or past major affective disorder, a proportion that did not differ significantly from that of a comparison group of female bulimic subjects (actual data not reported).

The differential diagnosis of bulimia is similar in males and females except for consideration of the Kleine-Levin syndrome (94), a rare condition that occurs predominantly in young men. Its symptoms include recurrent periods of hypersomnolence in association with excessive or compulsive eating, mood disturbances, and hypersexuality. The diagnosis of Kleine-Levin syndrome can usually be excluded by the consistent occurrence of binge eating without episodes of hypersomnolence.

## TREATMENT AND OUTCOME

Reports on the treatment and outcome of bulimia in males are insufficient to permit conclusions. Some investigators (12, 64) have reported anecdotal evidence of good outcomes with antidepressants, whereas others (62, 95) have reported relatively poor outcome with a combination of hospital treatment and psychotherapy. More recently, Levine et al. (96) found that 12 (80%) of 15 men in professionally led support groups for anorexic and bulimic men reported improvement of their eating disorder. The degree of improvement was not specified, and although roughly one-half of the subjects were bulimic, bulimia-specific analyses were not reported. Large trials with suitably matched comparison groups of female bulimic subjects have not been reported but are essential to defining the optimal treatment for bulimia in males.

## PATHOGENESIS AND SYNTHESIS OF FINDINGS

### *Biological Factors*

Several biological factors may contribute to the sex differences observed among bulimics. Boys reach puberty approximately 2 years later than girls (97), which may explain the later onset of bulimia in males (since boys tend to be confronted with the challenges of adolescence later than do girls) and the lower prevalence of bulimia among males (since males have more time to prepare themselves emotionally and cognitively for these challenges). In addition, the effect of the growth spurt at puberty is different for boys and girls (98). Whereas girls' increase in weight is largely due to extra adipose tissue, thereby tending to result in a body type that is culturally undesirable (67), in boys it is due to more muscle mass, resulting in the mesomorphic body type that most males desire (66). Thus, most boys enjoy a physiologically determined source of protection against the negative body image that may lead to bulimia. Because obesity negates this protective factor, the finding of an association between premorbid obesity and bulimia in males is not surprising.

Striegel-Moore et al. (67) have pointed out that males have a higher basal metabolic rate than females and that this might make males more successful dieters. Thus men, who are less likely than women to initiate a diet in the first place, may be relatively protected from the frustrations of a failed diet and therefore less likely to resort to more extreme weight-reducing measures, such as purging. Others have suggested that women's cyclic hormonal status may put them at greater risk than men for bulimia. Evidence to support this notion is scant, however, as studies that have attempted to demonstrate a relationship between binge eating and the menstrual cycle have yielded inconsistent results (60).

There is continuing controversy over the relationship between depression and bulimia. Although the authors of a recent review (99) concluded that depression and bulimia are two different disorders, they still may be causally related. If depression does tend to increase one's risk of bulimia, then this phenomenon might occur more often in women, whose prevalence of depression is higher than that of men (*DSM-III-R*).

### *Psychological Factors*

Psychoanalytic explanations of bulimia vary with the theoretical orientation of the author (100). Although it is beyond the scope of this article to review all such approaches, Schwartz (101) has identified two major themes. In the object relations view, a developmental arrest in the practicing subphase of separation-individuation is thought to lead to continued use of the body as a transitional object; binge eating and purging then recreate the infantile struggles with the mother during separation-individuation. The structural view emphasizes bulimia as a compromise solution that defends against anxieties brought about by intrapsychic conflicts. The few psychoanalytic discussions of bulimia in males have in fact combined both the object relations and structural perspectives (102, 103).

It is unclear from a psychodynamic viewpoint why males would be relatively protected from bulimia. Tabin and Tabin (104) have emphasized that the normal developmental tendency in boys is to identify with their fathers in the formation of both early gender and ego identity. To the extent that this is true, it may tend to protect boys from becoming pathologically involved in separation-individuation issues with their mother. If the family constellation included a distant or otherwise unavailable father, one might then expect this hypothesized developmental protection to be attenuated; consistent with this speculation, two studies noted distant or disrupted relationships between bulimic sons and their fathers (62, 89), but more detailed case reports are lacking.

The increased prevalence of homosexuality among male bulimics may simply reflect a cultural emphasis on appearance among homosexual men. Some psychoanalytically oriented investigators, however, have cited case studies suggesting that some of the family dynamics giving rise to eating disorders in males may also tend to cause conflicts over gender and sexuality (102, 103, 105). The evidence for this model is limited, and indeed it remains speculative whether any specific family constellation can be linked to the development of homosexuality (79).

Homosexuality may also predispose to bulimia by acting as a psychological stressor in homosexual adolescents. The discovery of homosexual feelings (106), combined with the realization that these feelings are not socially sanctioned, may act as yet another source of stress. When added to the many other challenges during this stage of life, homosexual identity formation may lead some adolescent boys to adopt bulimia as a means of coping (62).

Males may also be protected from bulimia according to a cognitive perspective. Polivy and Herman (65) have theorized that dieting causes binge eating by replacing the biological drive to maintain body weight with cognitive regulations of eating behavior. A variety of psychological and situational factors, such as depression or stressful events, can then disinhibit these cognitive controls of eating, leading to binge eating. Such a framework predicts that females and overweight males are at greater risk of starting a cycle of dieting, binge eating, and purging, given that both groups are more likely to diet than normal-weight males (56, 67, 68, 72).

### *Cultural Factors*

The striking sex difference in the prevalence of eating disorders has been cited frequently as evidence for a cultural cause (67), and much of the evidence reviewed here supports this position. Several cultural factors protect males from bulimia; perhaps most central are the differences between male and female ideal body types. Most males' ideal body type is the muscular mesomorphic physique, which is seen by both sexes as the embodiment of stereotypically "masculine" traits, such as independence and aggressiveness (66). When young people are shown pictures of thin (ectomorphic) men, they describe such men negatively, ascribing to them such traits as laziness, stupidity, and loneliness (107). Among females, however, the ectomorphic physique is associated with femininity, popularity, and success (67). Accordingly, dieting has two very different implications for males and females; for females, dieting propels them toward their ideal body, whereas for normal-weight males, dieting moves them further from their mesomorphic ideal. Thus, males are culturally discouraged from engaging in one of the prime precipitants of bulimia (65). Binge eating, on the other hand, is more socially sanctioned among males (4, 5). Not only might this explain the relatively high prevalence of binge eating among males, but it may also explain the lesser tendency for binge eating to result in overt bulimia in males, since it is less likely to induce guilt and subsequent purging.

The higher prevalence of bulimic behaviors and attitudes among homosexual men and men in certain occupations and athletic pursuits lends further support to a cultural explanation of bulimia. All of these subcultures share an increased concern about body weight, either for the sake of appearance (as among homosexual men) or for the sake of professional success (as among athletes and entertainers). From a sociocultural standpoint, these particular men may then have a risk for bulimia that is similar to the risk for females, although their overall risk may still be lower owing to biological or psychological factors.

## CONCLUSIONS

An extensive search of the English-language literature on bulimia in males revealed that the disorder affects approximately 0.2% of adolescent boys and young adult men and that males account for 10%–15% of all bulimic persons identified in community-based studies. Male patients account for only 1%–11% of the subjects in clinical series, however, a finding which suggests that clinic-based analytic studies may be subject to sampling bias. Nonetheless, male bulimic patients in clinic-based studies appear to have a later age of onset and to have higher prevalences of premorbid obesity, homosexuality, and asexuality than female bulimic patients; the lower marriage rate among bulimic men is consistent with the sexuality findings. Studies of concomitant substance abuse have yielded equivocal findings, although there is preliminary evidence that cocaine use may be a more important risk factor for males than for females. The clinical features of bulimia are similar in males and females, although male bulimic patients appear to be less concerned with strict weight control than female bulimic patients; there is also preliminary evidence that male bulimics may be less troubled by their binge eating. Both groups appear to have a a higher than average prevalence of affective, anxiety, and personality disorders. Conclusions about treatment and prognosis are premature because of the paucity of research in these areas.

Given the wealth of prevalence data reviewed in this article, we believe that further prevalence studies of bulimia and bulimic behaviors in males would be less valuable than analytic studies designed to elucidate the essential characteristics of bulimia in males. Although prospective studies are generally considered superior for clarifying etiologic relationships, in the case of a relatively uncommon condition, such as bulimia in males, such studies are unlikely to be feasible. Well-designed case-control studies, on the other hand, with suitably matched comparison groups of female bulimic and male nonbulimic subjects, would be practical and permit simultaneous testing of a number of unanswered questions. For example, to what extent do binge eating and purging put males at risk for bulimia? How are homosexuality and asexuality related to the etiology of bulimia in males? Is there a sex-specific association between substance abuse and bulimic behaviors? Do particular athletic and occupational pursuits actually place males at greater risk of bulimia? To what extent do family patterns differ between bulimic males and females? Do male and female bulimics differ with respect to concurrent psychiatric illness? Are certain treatment approaches more appropriate for male bulimics, as compared to female bulimics, and what is the long-term prognosis for this bulimia subgroup? Consideration of these questions and of the methodologic issues discussed throughout this review will improve our limited understanding of bulimia in males and may provide insight into the nature of the disorder in both sexes.

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# Menopause-Related Affective Disorders: A Justification for Further Study

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*Despite descriptions dating back to the nineteenth century of menopause-related affective syndromes, recent investigations have been unable to characterize a specific disturbance of mood or behavior related to this period of life. In this article the authors identify a number of methodologic problems in earlier studies and suggest that further study is warranted and that it is premature to conclude that menopause-related affective syndromes do not exist. They then provide guidelines for examining mood and behavioral changes that take place during the climacteric and menopause, with the hope of stimulating further research which may determine whether menopause-related affective disorders exist and, if so, their characteristics.*

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For centuries medical observers have described an association between disturbances of mood and behavior and changes in the reproductive endocrine system. These observations have reflected beliefs about the existence of a special relationship between the CNS and the reproductive endocrine system. Warnock (1) in 1890 stated, "The connection between the reproductive nerve centers and the higher psychical centers in the brain is so intimate, and the effect of menstruation on the vascular system is so marked, that a priori we should expect menstrual derangement to cause corresponding disturbances in the brain, both through the nervous and vascular systems." Similarly, the cessation of menstrual cycle function during menopause was also considered to be associated with alterations in mood and behavior. Fothergill has been cited (2) as one of the first medical observers (in 1776) to describe the disorders of the climacteric, including disturbances of mood and behavior. Nonetheless, despite long-standing medical interest, alterations of mood and behavior associated with the cessation of female reproductive function have been poorly characterized, if not dismissed, largely as a product of the following methodologic problems: 1) restrictive presuppositions about the characteristics of the affective or behavioral disturbance (e.g., conceptualized as endogenomorphic depression), 2) confusion of affective symptoms with affective syndromes, 3) failure to obtain adequate biologic evidence of ovarian dysfunction in defining climacteric or menopausal subjects, and 4) confusion of causation with association.

In this article we review the development of the concept of menopause-related mood and behavioral syndromes and discuss recent studies that have failed to support the existence of "involutional melancholia." We identify methodologic problems that complicate the interpretation of earlier studies and that must be addressed in future studies of these disorders. Finally, we suggest criteria for an operational definition of a climacteric- or menopause-related affective syndrome, with the hope of stimulating a reevaluation of earlier studies and pursuit of further understanding of the relation between reproductive endocrine change and disturbances in mood and behavior.

## HISTORICAL DEVELOPMENT OF THE CONCEPT OF MENOPAUSE-RELATED AFFECTIVE DISORDERS

Debates about the existence of menopausal affective disorders date back at least 90 years. William Conklin (3) described a variety of mood and behavioral symptoms in relation to menopause:

> The peculiar nervous instability of the climacteric woman is aptly described by that word...neurasthenia, the symptoms of which are so variable and ill defined as almost to defeat the attempt to marshal them into order. Sunshine and shadow rapidly chase each other over her daily life. She is self-sacrificing in the performance of duty at one time and, again, is querulous, vacillating in purpose and capricious in temper. She is oppressed by fears of impending evils, and grows moody, when she becomes a veritable Jacques, with a melancholy of her own, compounded of many simples, extracted from many objects. She is tortured by bodily pains equally hard to bear. There is scarcely an arrow in the armory of pain that is not unsheathed at this period.

Conklin also described a variety of menopause-related physical symptoms, including distressing feelings of heat as well as visceral "neuroses" related to the heart and gastrointestinal tract.

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In addition to the appearance of case reports verifying Conklin's description of neurasthenia-like disorders during menopause, medical observers suggested that at least one other distinct mood and behavioral syndrome existed in association with menopause. A special form of melancholia occurring during the climacteric was described, commencing a controversy in psychiatry that has lasted well into this century and has overshadowed attempts to explore further other menopause-related affective syndromes. Maudsley described this melancholia as "profound with vague delusions of an extreme character, that the world is in flames, that it is turned upside down, that everything is changed, or that some very dreadful but undefined calamity has happened or is about to happen. In some cases transient paroxysms of excitement break the melancholic gloom" (4). The depression described by Maudsley in England was also described in Germany by Kraepelin in 1896 (5) as a form of involutional melancholia. Although Kraepelin's description of involutional melancholia was not confined to women, the clinical presentation he described resembled that in Maudsley's description of climacteric melancholia: a particularly rigid and obsessive personality, no history of depression before the involutional period, no episodes of mania (distinguishing this disorder from manic-depression), a cross-sectional presentation with an agitated depression and hypochondriacal or nihilistic delusions, and a variable outcome.

Both Kraepelin and Maudsley excluded involutional melancholia from manic-depressive psychosis and considered it a separate entity with a variable prognosis. In 1907 Dreyfus (6) reviewed Kraepelin's observations and demonstrated the eventual recovery of a group of patients with involutional melancholia, unless dementia intervened, which led Kraepelin to concede to the classification of involutional melancholia as a form of manic-depressive illness in the eighth edition of his textbook (7). Hoch and MacCurdy (8) later challenged Dreyfus's observation that patients with involutional melancholia frequently recovered, and on the basis of the Kraepelinian criterion of longitudinal outcome, they argued in favor of the validity of involutional melancholia as a distinct diagnostic entity.

Following Bleuler's description of schizophrenia (9), with his emphasis on cross-sectional "symptomatology" rather than outcome, involutional melancholia was reestablished as an independent diagnostic entity, primarily as a result of papers by Titley (10) and Palmer and Sherman (11). The separateness of this syndrome was postulated on the basis of the different symptoms, different age at onset of the index episode, different premorbid personality, and different family history. For example, Stenstedt (12) examined 237 women with involutional melancholia and identified only 21 who experienced single episodes of melancholia confined to the menopause. However, it was observed that the patients with menopause-related involutional melancholia exhibited less severe symptoms and had a lower risk of affective disorder in family members than the other patients with involutional depression.

An affective disorder called involutional psychotic reaction appeared in *DSM-I*. However, as shown in a review by Rosenthal (13), the controversy persisted, and several prominent critics, such as Roth (14) and Redlich and Freedman (15), stated that the concept of a special involutional pattern of endogenous depression was no longer tenable. A distinctive syndrome was still described by Henderson and Batchelor (16) and Noyes and Kolb (17). Recent studies have not confirmed the existence of involutional melancholia or identified an increased prevalence of major depressive disorder during menopause. Nonetheless, these studies have not disproved a relationship between depression and menopause in women who experience depression in this context. Further, several studies have suggested that in some women menopause conveys an increased vulnerability to the onset of other forms of affective disorder, such as bipolar disorder (as Angst [18] proposed), and that menopause may interact with and alter the course of primary affective disorder (19). Finally, the occurrence of neurasthenia or atypical depression associated with menopause, described in early case reports, has been largely ignored.

## MORE RECENT INVESTIGATIONS OF INVOLUTIONAL MELANCHOLIA

In general, the evidence that has been adduced to refute the existence of involutional melancholia is epidemiologic and phenomenologic. Weissman (20) studied a sample of 422 consecutive female outpatients admitted with diagnoses of major nonbipolar depression. Using only an age criterion of 45–55 years for defining menopausal status, Weissman found no difference in symptom patterns and number of previous depressive episodes between the 347 women younger than 45 years of age (presumed premenopausal) and the 75 women older than 45 years (presumed menopausal or postmenopausal). Weissman concluded that there was not sufficient evidence to consider involutional-onset depression as a distinct entity. In agreement with Weissman's findings, studies have not demonstrated a greater risk of suicide or psychiatric hospitalization for women during the climacteric or postmenopausal years (21). Further, despite a generally higher prevalence rate of depression in women than in men, studies in the past decade have reported a slightly lower 6-month prevalence rate of depression during the presumed menopausal/climacteric years than in younger age groups (22, 23).

In summary, several studies provided evidence against the validity of the involutional melancholia construct by indicating that 1) there appeared to be no distinct symptom pattern, 2) there was no distinct pattern of previous episodes of depression in patients with menopause-related major depressive episodes, 3) there was no increased risk of suicide or psychiatric hospitalization during the menopause period, and 4) there appeared to be no increased prevalence of depression during menopause. However, this evidence is far from conclusive in refuting the existence of a menopause-related affective syndrome. Despite similar or lower point prevalence rates and similar clinical presentations of depression during menopause and at other times of life, one cannot infer that these syndromes share identical etiologies. Both Stenstedt (12) and Brown et al. (24) reported that involutional-onset depression was associated with a lesser family history of depression than was found for patients with early-onset depression. Further, in the study by Weissman (20), 47% of the menopausal and 65% of the postmenopausal depressed women (as defined by the age criterion) had no previous history of depression. While the prevalence of histories of primary depression was not significantly in excess of that seen in the younger age group (44%), the substantially greater period of risk of developing an episode of depression in the menopausal/postmenopausal group is potentially important. Thus, while menopausal major depression does not appear phenomenologically distinct, there is evidence suggesting that it may differ from earlier-onset depression with respect to the patient's family history and age at the time of the first depressive episode. It is not unusual in medicine for phenomenologically similar disorders to have different precipitants or causes; for example, meningitis in both the neonate and the infant may present with fever, vomiting, and drowsiness, yet different pathogenic organisms are typically involved for the two age groups.

Even if major depressive disorder is not more prevalent during menopause, other forms of affective disorder may be associated with this period. In fact, many of the original reports described a clinical picture during menopause that was more consistent with neurasthenia or atypical depression. The presupposition that menopause-related affective syndromes, if they exist, will be manifested by melancholia may have interfered with the identification and characterization of other affective syndromes (e.g., atypical depression) occurring at this time. This suggestion is supported by some studies that have examined the prevalence of affective symptoms in menopausal women.

Winokur (25) studied a sample of 71 consecutive women with admission diagnoses of affective disorder and identified, on the basis of at least a 3-year history of amenorrhea preceding admission, 28 patients who were menopausal. Winokur compared the risk of hospitalization for a depressive episode during the 3 years after menopause in these 28 patients with the overall risk of developing an affective syndrome between ages 20 and 80 in the total sample of 71 women (i.e., the total number of depressive episodes divided by the number of years at risk). As there was no significant difference between the risk of depression during the 3 years after menopause and during the entire period of risk (ages 20–80), Winokur drew the following conclusions: 1) his data did not support the idea of menopause as an important factor in precipitating an episode of affective disorder, 2) affective disorders are not more likely to occur during menopause, and 3) the study of menopause-associated depression is unlikely to promote further understanding of affective disorder.

It appears, however, that Winokur used different severity criteria for the diagnosis of depression during menopause than for depressions that were not menopause related, because of the high frequency with which symptoms of depression (38%) and nervousness (75%) were reported to occur during menopause in his sample of patients. The use of more stringent diagnostic criteria for depression (e.g., need for hospitalization) during the 3 years after menopause would tend to decrease spuriously the calculated risk rate for the development of an affective disorder in the 3 menopausal years. Further, Winokur stated that since the symptoms reported during menopause were "similar to those which patients suffering from affective disorder complain of," the addition of the hospitalization criterion was necessary. Thus, given the high frequency of reports of menopause-related affective symptoms in this group, it seems unwarranted to conclude that there is "little value in looking specifically at the menopausal state for clues to the etiology of ordinary affective disorder." Additionally, even if the menopause-related symptoms were phenomenologically distinct from major affective disorder, the affective symptoms occurring so frequently during menopause require further explanation.

Several studies have examined the prevalence of mood and behavioral symptoms in larger samples of women experiencing the climacteric and menopause. Some (26–28) but not all (29) have found an increased prevalence of depressive symptoms related to the climacteric and/or menopause. In a serial cross-sectional-design study of 477 women, Kaufert and Gilbert (30), using patients' self-reports of menstrual cycle irregularity or amenorrhea to define menopausal status, found a high prevalence of clinically significant affective disorders during the 3 years surrounding menopause. Although these investigators did not identify by factor analysis a specific pattern of affective or somatic symptoms associated with menopause, they did observe that during the 3 years around menopause, 30% of their sample scored higher than 16 on the Center for Epidemiologic Studies Depression (CES-D) Scale (scores greater than 16 are associated with the diagnosis of major depression or primary anxiety disorder). McKinlay et al. (31) also used the CES-D Scale in a single cross-sectional-design study of 2,500 women and relied on patients' self-reports of menstrual cycle irregularity or amenorrhea to define menopausal status. McKinlay et al. did not observe a greater prevalence of affective disorders, as defined by the CES-D Scale, during menopause than in other periods of life. They did, however, identify in their sample an association between physical symptoms and mood disorder as defined by that scale. Further, these investigators observed that mood disorder as defined by the CES-D Scale occurred twice as frequently in the group of women with artificial or surgical menopause as in the other menstrual status groups.

Thus, menopause does not appear to be uniformly characterized by disturbances in mood and behavior, nor is there a uniform and consistent menopause-related affective syndrome. Nonetheless, the climacteric and menopause (surgically induced and natural) do appear to be associated with an excess of somatic, mood, and behavioral symptoms, and some studies have found an increased vulnerability to affective disorders during this period of life. Unfortunately, there has been no prospective longitudinal study examining the development of mood and behavioral complaints within individuals in relation to the onset of the climacteric or menopause. Further, no study has examined the phenomenology of mood and behavioral syndromes, other than involutional melancholia or major depressive disorder, occurring during menopause, and it remains unclear whether patients with menopause-related affective syndromes have family histories, biological and treatment response characteristics, or longitudinal clinical course characteristics that distinguish them from patients with affective syndromes occurring at other times of life. For example, are panic disorders that appear to develop *de novo* in association with hot flashes similar in all phenomenologic and historical respects to primary panic disorder? Additionally, it is not clear whether hot flashes and other hypoestrogenic symptoms are consistently associated with mood and behavioral disturbances.

Thus, when one is faced with the differential diagnosis of a menopausal woman with psychiatric symptoms, one must consider the following: 1) whether the person is indeed menopausal (discussed in the next section), 2) whether the mood and behavioral symptoms are secondary to menopause-associated somatic symptoms, and 3) whether the mood and behavioral syndrome constitutes the *de novo* occurrence of a primary psychiatric disorder or the exacerbation of a psychiatric syndrome by menopause. For research purposes, this last issue may warrant further attention.

## METHODOLOGIC PROBLEMS OF EARLIER STUDIES THAT MUST BE ADDRESSED IN FUTURE STUDIES

### *Operational Definition of the Menopausal Affective Syndrome*

By specifying a pattern of symptoms, a minimum duration, a minimum level of overall severity and impairment, and a required temporal linkage to a specific period of reproductive endocrine change, an operational definition of a menopausal affective syndrome can be formulated. This would permit the differentiation of affective *symptoms* occurring in association with menopause from a menopausal affective *syndrome*, thus facilitating the selection of homogeneous samples for research purposes. A menopausal affective disorder can be defined as the occurrence of affective and behavioral symptoms that are sufficiently severe to interfere with some aspects of life and that appear with a specific relationship to the menopausal period, i.e., during the perimenopause or menopause.

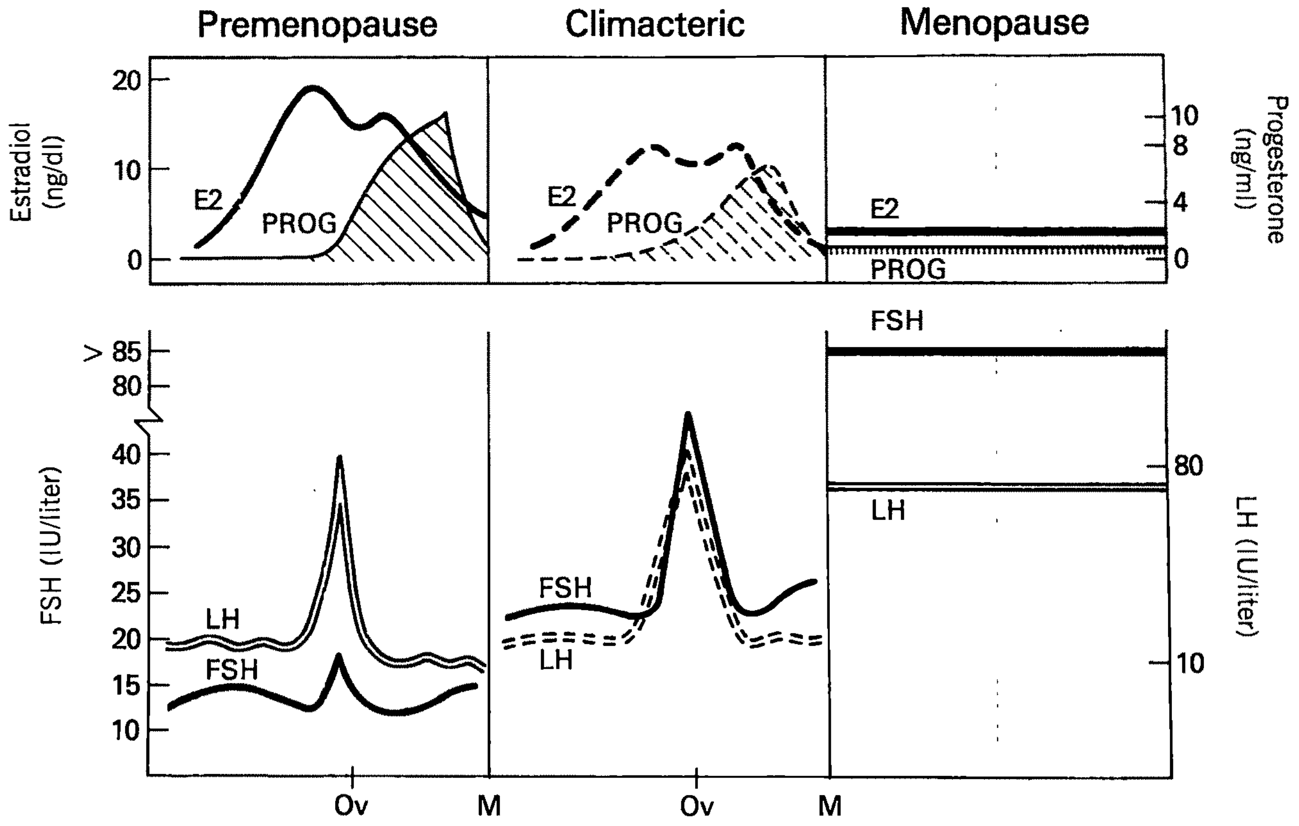
### *Nature of the Affective and Behavioral Symptoms or Syndromes*

Among studies of menopause, there is a general tendency to confuse reports of psychiatric symptoms, which can be multidetermined, with the presence of clinically verifiable psychiatric syndromes that may require relatively specific therapeutic interventions. Most psychometric instruments used to detect or confirm a psychiatric illness contain both somatic symptoms and mood and behavioral symptoms. These instruments may be useful in recording symptoms typically associated with a depressive illness but cannot be used to diagnose the existence of a depressive illness. Distinguishing between mood or behavioral symptoms and syndromes requires that measures of impairment, severity, and pervasiveness be included in the description of the syndrome. Problems in this area have included failure to measure the severity and duration of symptoms (32), attribution of clinical importance to symptoms without adequate measures of the associated distress or impairment (29), and use of scales with insufficient sensitivity to differences in severity (i.e., that rate symptoms only as present or absent) (33–36). Further, the use of excessively stringent criteria for severity may result in failure to identify clinically significant mood disturbances during menopause (25). Until more objective parameters are available, measures of impairment should permit the investigator to demonstrate that, in a menopausal affective syndrome, it is the affective and behavioral complaints which constitute the prominent source of the patient's distress and which are associated with some form of dysfunction in her life.

### *Methods of Establishing the Linkage of Symptoms With Menopause*

Without a clear onset of symptoms at the time of menopause, the menopausal affective syndrome cannot be meaningfully said to exist independent of affective disorders occurring at other periods of life. Unfortunately, the climacteric and menopause are not unitary biologic events suitable for cross-sectional definition. The World Health Organization defined menopause as the permanent cessation of menstruation resulting from loss of ovarian activity, and the climacteric or perimenopause was defined as the period of transition from reproductive to nonreproductive status, i.e., the period immediately before menopause and at least the first year afterward (37). For research purposes, menopause and the climacteric remain ill-defined periods associated with complete and partial ovarian failure, respectively. If mood changes are to be evaluated in the context of reproductive endocrine change, then, as de Lignieres and Vincens have suggested (38), the stage of reproductive life should be well characterized endocrinologically. Specifically, women in the climacteric must be distinguished from women in the postmenopausal period. A variety of measures have been used to identify climacteric or menopausal status: age (20, 23, 32); patients'

**FIGURE 1. Levels of the Ovarian Steroids Estradiol (E2) and Progesterone (PROG) (top) and the Pituitary Gonadotropic Hormones Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH) (bottom) at Three Phases of Reproductive Life[a]**



[a]Ov=ovulation; M=menses. The illustrated hormonal patterns for the climacteric do not reflect intra- and interindividual variability in frequency of ovulation and length of menstrual cycle during this phase.

self-reports of at least 1 year of amenorrhea (indicating menopause) (29, 33–35, 39) or irregular menstrual cycles (indicating the climacteric) (29, 34, 35, 39); and hormone levels.

Although the mean age at menopause has been established as 50–51 years, there is a wide range of reported age at onset, from 41 to 59 years (40). Thus, selecting a particular age group for research could result in a heterogeneous group of women, some in the climacteric, some menopausal, and some with normal menstrual cycle function. This was obviously a significant problem in many earlier epidemiologic and phenomenologic studies. Further, an endpoint in the number of years past menopause must be defined, since a mood disorder occurring 10 years after menopause cannot be meaningfully described as menopause related.

Several studies (29, 34, 35, 39) have defined menopause by patients' reports of a preceding period of 1 year of amenorrhea. However, as noted by Treolar (40), a patient's retrospective report of the terminal menstrual flow may misrepresent her age at menopause, since (among other things) dysfunctional uterine bleeding occurs in some postmenopausal women. Further, retrospective self-reports of the onset of the climacteric, defined as the beginning of menstrual irregularity in middle-aged women, are subject to reporting bias and possible misattribution. Despite reports that the climacteric is characterized by increasing variability in the menstrual cycle (40), several factors make a history of increasing menstrual cycle irregularity an imperfect diagnostic criterion for the climacteric. These factors are the following: 1) in the last 18 months preceding menopause, 40% of the menstrual cycles in a sample of women will be within the normal range of 21–35 days (41); 2) variability in the menstrual cycle is not confined to the climacteric (40, 41); 3) an undetermined number of women may enter menopause without any uncharacteristic menstrual cycle irregularity (40); and 4) proposed definitions of the duration of the climacteric, based on menstrual cycle phase irregularity, range from 1 to 10 years (40).

Hormone levels have been used with some degree of success to define menopause (figure 1). During the climacteric and menopause, the ability of the ovaries to produce estradiol, the main form of ovarian estrogen, declines, resulting in marked increases in follicle-stimulating hormone (FSH) and, to a lesser extent, luteinizing hormone. Levels of FSH that are consistently elevated (greater than 25 IU/liter) when sampled at several points during the menstrual cycle, combined with at least a

6-month history of menstrual cycle irregularity, may serve as biologic evidence of the climacteric. Similarly, FSH levels greater than 40 IU/liter plus a 6-month history of amenorrhea appears to be a reasonable criterion for selecting a homogeneous sample of menopausal women. However, one study (42) found that serum estradiol/estrone ratios were within the premenopausal range in three of 12 amenorrheic patients with FSH levels greater than 40 IU/liter, suggesting residual ovarian estrogen production and only partial ovarian failure. Thus, even when hormonal standards are used, the diagnosis of menopause may be uncertain.

## CONTEXT WITHIN WHICH SYMPTOMS DEVELOP DURING THE CLIMACTERIC AND MENOPAUSE

### *Historical Context*

A variety of etiologies were proposed during the nineteenth century to explain climacteric-associated mental illness, including the following: cerebral congestion or anemia, retention of poisonous material owing to the nonfunctioning uterus (4), abnormal intestinal fermentation (43), and reflex excitability secondary to ovarian dysfunction, as described by Farnham (44). One of the presumed mechanisms underlying this last relationship was summarized by Farnham in 1887 as follows: "The ovaries, after long years of service, have not the ability of retiring in graceful old age, but become irritated, transmit their irritation to the abdominal ganglia, which in turn transmit the irritation to the brain, producing disturbances in the cerebral tissue exhibiting themselves in extreme nervousness or in an outburst of actual insanity." These presumed etiologies gave rise to equally diverse treatments, including purgatives, faradic stimulation, potassium bromide (45), dietary supplements (46), and ovarian, thyroid, and cardia extracts (47).

Current theories of the etiology and treatment of menopausal mood disorders have reflected the following observations. First, mood symptoms occur in association with declining levels of estradiol; similar disturbances in affect occur after oophorectomy (48). In both cases, mood disturbances reportedly respond to hormone replacement therapy (38, 49). Second (the domino theory), mood symptoms may occur in response to distressing estrogen-sensitive somatic symptoms such as hot flashes or vaginal dyshidrosis, with a remittance of the mood symptoms following treatment of the somatic symptoms (50). Third, mood symptoms may occur in association with alterations in family roles, stressful life events, and the vicissitudes of aging (51).

### *Estrogen Withdrawal and Mood*

It has been postulated that affective disorders result from disturbances of central neurotransmitter activity. The manifold interactions between gonadotropins/gonadal hormones and neurotransmitters/neuromodulators (52, 53) suggest, therefore, a possible neurobiologic basis for the effect of alterations in reproductive hormone activity on mood and behavior. The transition from reproductive life to menopause represents a period of unmatched biologic variability. For example, as shown in figure 1, the normal menstrual cycle is characterized by brief periods of unopposed estradiol secretion during the follicular phase. In contrast, the climacteric may be associated with relatively longer periods of unopposed estradiol secretion due to more frequent anovulatory cycles, whereas menopause is characterized by low-to-absent estradiol or progesterone activity due to ovarian failure. This sequence of hormonal events is potentially significant, given that estradiol may have different actions in the same brain region depending on previous exposure to it (estradiol priming) or the presence of progesterone.

Estrogen alone has been found to alter brain neurotransmitter activity in several ways. As reviewed elsewhere (53), in the hypothalamus, estradiol has been reported to decrease norepinephrine synthesis, decrease glutamic acid decarboxylase activity (54), and increase muscarinic receptors (55). In ovariectomized rats, in the cerebral cortex, estradiol replacement decreases β-adrenergic and serotonin receptors (56). Estradiol alters the excitability of hippocampal pyramidal cells in vitro (57, 58) and lowers the threshold for electrically induced seizures in the medial amygdaloid nucleus (59). An antidopaminergic effect of estrogen at both the pituitary and the striatum has been described (60). Consistent with this last finding is the observation that L-dopa-induced tardive dyskinesia improved with estrogen treatment (61). Conversely, it should be noted that enhanced dopamine receptor sensitivity after administration of estrogen has been reported (62, 63). It has been observed that regional brain monoamine oxidase activity is increased by progesterone (64) and decreased by estrogen (65).

The extent to which gonadal hormones, gonadotropins, catecholamines, and neuropeptides may interact in the development of climacteric/menopause-related mood and behavioral disorders is purely a matter for speculation. Nonetheless, it seems clear that changes in reproductive endocrine function would be accompanied by discrete but widespread alterations in the CNS neurotransmitter activity that may comprise relevant mechanisms in the pathophysiology of mood disorders. Further, the rate of hormonal changes may be an important regulatory variable, perhaps conveying a differential sensitivity to sudden (surgically induced menopause) versus gradual (natural menopause) decline of ovarian function.

### *Domino Theory*

The manifold effects of estrogen on the CNS have led to therapeutic trials of estrogen in both affective disorders (66, 67) and menopausal syndromes (68). While beneficial effects on physical and emotional symptoms have been observed after the administration of estrogen in patients with menopausal syndromes, one cannot necessarily infer a direct effect of changes in estradiol on mood. For example, it is unclear whether the reported improvement represents treatment of the primary menopausal affective syndrome or a reduction in affective and behavioral symptoms secondary to improvement of concurrent hormone-sensitive physical complaints (e.g., sleep disturbance secondary to nocturnal hot flashes). Similarly, somatic symptoms experienced during menopause may result in behavioral or affective disturbances that may create considerable diagnostic confusion in the assessment of a menopausal syndrome. For example, some women with severe daytime hot flashes report social avoidance similar to that observed in agoraphobic or social-phobic patients. Thus, failure to inquire about menopausal symptoms may lead to the misdiagnosis of primary anxiety disorders, with specific therapeutic consequences. Further, affective symptoms occurring in association with menopausal symptoms may alter the patient's perception of the severity and disability associated with somatic symptoms of estrogen deficiency.

### *Relation to Life Stage*

Studies have also identified the importance of social factors and life stress during this period of a woman's life (69). These psychosocial factors include 1) alteration in family roles, 2) a changing social support network, 3) interpersonal losses, and 4) aging and the onset of physical illness. Correlational analyses of selected variables, such as stressful life events, with mood ratings may be useful in identifying factors associated with menopausal symptoms. However, a causal role for psychosocial factors in the mood syndromes with which these factors are associated has not been demonstrated. Middle age, and in particular the climacteric or menopause, is not uniformly characterized by illness, widowhood, an empty nest syndrome, or becoming a grandparent (70). These may be common events, but they are not confined to middle age, nor are they universal occurrences at middle age. Furthermore, models describing menopause as a life crisis may misrepresent the negative impact of this developmental state or at least the universality of such an impact (31). Finally, it is unclear which factors determine personal response to crisis, whether it is positive, resulting in goal achievement or mastery, or negative, resulting in symptoms of emotional distress, low self-esteem, and depression (51). Nevertheless, the systematic evaluation of psychological and social factors in the context of menopause will provide valuable information about the importance of these variables in the normal aging process as well as their role in the development of menopause-related affective disorders.

## TREATMENT RECOMMENDATIONS

The management of mood and behavioral disturbances during menopause requires determining the symptoms experienced and the hormonal context in which they appear. As a complement to the careful neuropsychiatric evaluation that is usually recommended, longitudinal monitoring of symptoms on a daily basis may provide invaluable information about the severity, stability, and pattern of symptom experience. Both affective symptoms and relevant somatic symptoms (e.g., vaginal dryness, hot flashes) should be monitored. If not previously done, measures of FSH and estradiol should be made in order to document the presence of menopause and hypoestrogenism.

In the case of a major depressive disorder, the therapy selected should reflect the nature of the menopause (natural or surgically induced), the nature and severity of the somatic symptoms, and the presence (or absence) and type of hormone replacement therapy. In patients with natural menopause who present with depression, the presence of signs of estrogen deficiency should lead first to consideration of a trial of hormone therapy, unless there are contraindications to estrogen replacement (e.g., a history of breast cancer). Alternatively, if menopausal somatic symptoms are mild or minimal despite laboratory evidence of hypoestrogenism and the presence of moderate to severe mood symptoms, then the choice of hormone replacement versus antidepressant therapy may be best informed by such factors as past personal history of depression, family history of affective disorder, or the presence of contraindications to estrogen replacement.

In a patient experiencing a surgically or medically induced menopause, the impact of the condition necessitating the oophorectomy should be meticulously evaluated. Additionally, the relationship between the onset of symptoms and the initiation of hormone replacement therapy should be determined for at least two reasons. First, mood and behavioral symptoms may result from inadequate estrogen replacement and can remit with appropriate adjustments of dosage or with a change to an alternative form of estrogen replacement (e.g., estradiol versus conjugated estrogens). Therefore, it is recommended that hormone replacement therapy be adjusted before adjunctive psychopharmacotherapy is considered. Second, mood and behavioral symptoms may be a direct result of hormone replacement therapy. Specifically, cyclic mood and behavioral symptoms have been reported in association with sequential hormone replacement and may remit with a change in the replacement regimen from sequential to continuous combination therapy. Symptoms of depression and loss of libido consequent to therapeutically induced ovarian failure may, nonetheless, be responsive to antidepressant therapy.

## CONCLUSIONS

The existence of a specific climacteric- or menopause-related affective syndrome remains controversial despite reports since the eighteenth century of an association between disturbances in affect and behavior and this period of reproductive life. Conclusions that no menopause-related mood syndromes exist reflect, at least in part, selective interpretation of the data, lack of methodologic precision, and failure to consider that affective syndromes other than major depressive disorder might be associated with the climacteric and/or menopause. Recent advances in reproductive endocrinology research continue to clarify the neurobiology of the menopause process and will enhance our understanding of the role of declining ovarian function in the production of menopause-related affective and behavioral symptoms. It is within this context of greater understanding of reproductive endocrinology that we have a unique opportunity to reexamine menopause-associated affective syndromes in a way that will possibly advance both our therapeutic precision and our understanding of the relevance of endocrine change to behavioral state.

Prospective longitudinal monitoring of mood change in relation to change in reproductive endocrine function will help clarify the natural course of menopausal affective disorders. It will also inform us of the premorbid factors that may contribute to the development of these disorders, the prevalence and the nature of affective disturbances arising *de novo* during menopause or the climacteric, and the effects of life events and concurrent physical symptoms on patients' experience of menopause-related affective disorders.

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# The Future of Psychiatry: Psychiatrists of the Future

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*Objective: The authors' goal was to examine the changing demographic trends in psychiatry manpower. These changes have important implications for the practice of the profession in the future. Method: Each year, the APA Office of Membership, in collaboration with the American Association of Directors of Psychiatric Residency Training, conducts a census of all residents in psychiatry. A survey instrument is sent to the director of residency training in each U.S. program accredited by the Accreditation Council for Graduate Medical Education. Using data from this survey and from the American Medical Association, the authors conducted a study of the changes in the number of psychiatric residents over the last decade, particularly the increases in the number and percentage of women in medicine and psychiatry. Results: They found that the number of psychiatric residents has grown from 4,674 in academic year 1978–1979 to 5,829 in 1987–1988, an increase of 25%. The percentage of women has increased from 32% of all psychiatric residents in 1978–1979 to 41% in 1987–1988. The largest proportions of female physicians and psychiatrists were found in the age groups younger than 35. Conclusions: Previously documented gender differences that affect practice patterns and career opportunities may very well change as a function of the increasing representation of women in the profession of psychiatry, and these changes need to be taken into account in planning for future patient care and research needs.*

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Most discussions of the future of psychiatry rightly focus on the content of the field, emphasizing scientific advances in diagnosis and treatment as well as the theoretical developments in neurobiology and psychosocial function. They convey a sense of excitement, discovery, and resources unparalleled in the history of the field.

In these discussions, there often is a striking omission. Psychiatry as a field depends heavily on the psychiatrists who provide care, undertake research, and educate others. As such, the future of the field is dependent on its manpower, and the needs of its manpower depend on two groups: psychiatrists already in practice and those about to enter the field—psychiatric residents and medical students.

Continuing medical education programs are a necessity for psychiatrists already in practice if they are to maintain and improve their knowledge and skills and keep up with the massive developments and changes in the field. Equally important, however, and often overlooked, psychiatric residents and the medical students choosing psychiatry represent the long-term shape and focus of the field. The successes and failures of psychiatry will be measured through their work.

It is still a commonly held belief that medical students are not interested in psychiatry, even though data on students graduating in 1980–1988 (1) have uniformly demonstrated increases in both the number and the percentage of U.S. medical students choosing psychiatry as well as an increase in the number of psychiatric residents. A 1988 survey of graduating U.S. medical students conducted by the Association of Amer-

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**TABLE 1. Number of Male and Female Psychiatric Residents and All Residents, 1978–1988[a]**

| Academic Year | All Residents[b] | | | Psychiatric Residents[c] | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Total | | Female | | Male | |
| | Total | Female | Male | N | % of All Residents | N | % of All Female Residents | N | % of All Male Residents |
| 1978–1979 | 63,163 | 11,839 | 51,324 | 4,674 | 7.4 | 1,489 | 12.6 | 3,184 | 6.2 |
| 1979–1980 | 64,615 | 12,431 | 52,184 | 4,452 | 6.9 | 1,553 | 12.5 | 2,898 | 5.5 |
| 1980–1981 | 61,465 | 13,738 | 47,727 | 4,545 | 7.4 | 1,636 | 11.9 | 2,909 | 6.1 |
| 1981–1982 | 68,217 | 16,040 | 52,177 | 4,681 | 6.9 | 1,723 | 10.8 | 2,958 | 5.7 |
| 1982–1983 | 69,142 | 16,341 | 52,801 | 4,886 | 7.1 | 1,842 | 11.3 | 3,044 | 5.8 |
| 1983–1984 | 72,397 | 17,566 | 54,831 | 5,109 | 7.1 | 1,914 | 10.9 | 3,195 | 5.8 |
| 1984–1985 | 75,125 | 18,603 | 56,522 | 5,312 | 7.1 | 1,996 | 10.7 | 3,312 | 5.9 |
| 1985–1986 | 74,514 | 19,562 | 54,952 | 5,488 | 7.4 | 2,133 | 10.9 | 3,347 | 6.1 |
| 1986–1987 | 76,815 | 20,746 | 56,069 | 5,508 | 7.2 | 2,241 | 10.8 | 3,257 | 5.8 |
| 1987–1988 | 81,410 | 22,623 | 58,787 | 5,829 | 7.2 | 2,402 | 10.6 | 3,413 | 5.8 |

[a] Includes all residents on duty as of September 1 each year.
[b] Data are from the AMA (4).
[c] Data are from the APA annual census of residents.

ican Medical Colleges (2) found that 591 (almost 6%) of the students who responded indicated that they were considering psychiatry or child psychiatry as their primary specialty choice. Of the 591 students who said that they were considering psychiatry, 444 (75%) had made this choice by their third year in medical school (3).

In this paper we focus on the changing numbers and demographic characteristics of the psychiatric resident population over the 10-year period from 1978 to 1988 and discuss implications of these changes for the future.

## METHOD

Each year, the APA Office of Membership, in collaboration with the American Association of Directors of Psychiatric Residency Training, conducts a census of all residents in psychiatry. A survey instrument is sent to the director of residency training in each U.S. program accredited by the Accreditation Council for Graduate Medical Education.

Residents are identified by name, and considerable demographic information about their previous medical education, age, sex, and specific aspects of training is obtained. The response rate is 100%, accomplished by personal contact with residency directors and department chairs. Thus, the census provides the most comprehensive listing of residents actually in training in the United States, as well as highly detailed information about the current and future shape of the field of psychiatry. In this paper we examine the census data obtained over the past 10 years, noting changes and trends, particularly increases in the number of psychiatric residents and shifts in gender distribution. A later report will address other demographic and training characteristics.

## RESULTS

### *Increase in the Number of Psychiatric Residents*

The number of psychiatric residents has grown from 4,674 in 1978–1979 to 5,829 in 1987–1988—an increase of 25% (table 1). This change can be largely attributed to an increase in female psychiatric residents, since their number has grown by 913 (61%), compared with an increase of 229 (7%) in male psychiatric residents during the same time period. (These data exclude 13 residents whose sex was not reported.)

The percentage of women has increased from 32% of all psychiatric residents in 1978–1979 to 41% in 1987–1988, in spite of the increase in the number of all psychiatric residents from 4,674 to 5,829 during the same years. The percentage of men has decreased from 68% of all psychiatric residents in 1978–1979 to 59% in 1987–1988. The number of male psychiatric residents has grown at a much slower rate than the number of female psychiatric residents, and the number of male psychiatric residents showed greater yearly variability than that of female psychiatric residents, ranging from a decrease of 9% between 1978–1979 and 1979–1980 to an increase of 5% between 1986–1987 and 1987–1988. Most of the increases in the number of male psychiatric residents have occurred since the 1982–1983 census.

Changes in the psychiatric resident population probably reflect the impact of the National Conference on Recruitment Into Psychiatry held in March 1980 (5) and the follow-up activities on its recommendations. Some of the major goals that emerged from the conference were to increase the likelihood that medical students would choose a career in psychiatry, to improve the quality of the psychiatric residency experience, and to emphasize the challenges and satisfactions of psychiatric practice. In addition, conference participants recommended increasing recruitment of female

**TABLE 2. AMA Age Groups of Male and Female Physicians, Psychiatrists, and Residents, December 1986**[a]

| Age Group (years) | Total | Men N | Men % | Women N | Women % |
|---|---|---|---|---|---|
| Younger than 35 | | | | | |
| All physicians | 142,328 | 106,418 | 74.8 | 35,910 | 25.2 |
| All psychiatrists | 6,063 | 3,949 | 65.1 | 2,114 | 34.9 |
| All residents | 70,016 | 51,274 | 73.2 | 18,742 | 26.8 |
| 35–44 | | | | | |
| All physicians | 162,461 | 135,056 | 83.1 | 27,405 | 16.7 |
| All psychiatrists | 9,361 | 7,129 | 76.2 | 2,232 | 23.8 |
| All residents | 9,540 | 6,541 | 68.6 | 2,999 | 31.4 |
| 45–54 | | | | | |
| All physicians | 102,665 | 91,716 | 89.3 | 10,949 | 10.7 |
| All psychiatrists | 7,755 | 6,448 | 83.1 | 1,307 | 16.9 |
| All residents | 812 | 513 | 63.2 | 299 | 36.8 |
| 55–64 | | | | | |
| All physicians | 80,321 | 74,032 | 92.2 | 6,289 | 7.8 |
| All psychiatrists | 6,344 | 5,500 | 86.7 | 844 | 13.3 |
| All residents | 108 | 76 | 70.4 | 32 | 29.6 |
| 65 and older | | | | | |
| All physicians | 81,385 | 75,268 | 92.5 | 6,117 | 7.5 |
| All psychiatrists | 3,201 | 2,762 | 86.3 | 439 | 13.7 |
| All residents | 0 | 0 | 0.0 | 0 | 0.0 |
| Total | | | | | |
| All physicians | 569,160 | 482,490 | 84.8 | 86,670 | 15.2 |
| All psychiatrists | 32,724 | 25,788 | 78.8 | 6,936 | 21.2 |
| All residents | 80,476 | 58,404 | 72.6 | 22,072 | 27.4 |

[a]Data are from the AMA (6).

and minority faculty members to provide appropriate role models.

### *The Feminization of Psychiatry*

By using data from the American Medical Association (AMA) (6), we can compare the percentage of female psychiatric residents with the proportion of female physicians, psychiatrists, and all residents. The AMA reported that there were 86,670 female physicians (15% of the 569,160 physicians in the United States) as of December 1986; however, women represented 25% of the physicians under age 35 (table 2). Similarly, female psychiatrists represented 21% of all psychiatrists, and women accounted for 27% of all residents (table 2). The AMA reported that female psychiatric residents represented 39% of all psychiatric residents (2,133 out of 5,488) (5). These figures correspond to those reported in the 1985–1986 APA psychiatric resident census (table 1). Women were thus more highly represented in the psychiatric resident population than they were among all physicians (including those younger than age 35), all psychiatrists, and all residents.

For the decade reported in this study—academic years 1978–1979 through 1987–1988—the number of women graduating from U.S. medical schools increased from 3,445 to 5,356, representing 23% of all graduates in 1978–1979 and 34% in 1987–1988 (6, 7). Similarly, the number of women in psychiatric residencies increased from 1,489 to 2,402 in the same time period, an increase from 32% of all residents in psychiatry in 1978–1979 to 41% in 1987–1988 (table 1).

The 1988 survey of graduating medical students conducted by the Association of American Medical Colleges (2) listed the gender distribution of its 10,379 respondents as 66% male and 33% female (1% unreported). Of the 591 students who reported that they chose psychiatry as their specialty, however, 275 (47%) were women. These figures lend support to the strong and continuing trend of an increase in the number of women choosing psychiatry as a specialty, although at slightly lower rates than the increase in the number of women in medicine. As shown in table 1, the number of female residents increased by 91% in the 10-year period, compared with an increase of 61% for female psychiatric residents, indicating that the growth rate for women in all medical specialty residencies was greater than that of women in psychiatric residency.

The distribution of all physicians and of female physicians in selected specialties in the period 1970–1985 is shown in table 3; these data are from the AMA (8). The increase in the percentage of female psychiatrists was smaller than the increases of female physicians in other specialties such as general practice (including family practice), general surgery, and internal medicine. Of course, the number of women in psychiatry was greater than the number of women in some other specialties, so similar numerical increases in psychiatry and in a surgical specialty, for instance, led to a larger percentage increase in the latter. The data in table 3 show that from 1979 to 1985 the percentage of female physicians rose from 8% to 15%; the percentage of female psychiatrists increased from 13% to 21%. Although the representation of female physicians is still variable among the specialties, these gender differences may be weakening. Psychiatry can no longer rely solely on the increasing number of women entering medicine; competing preferences for and availability of training in other specialties will have an impact on the future of psychiatry.

### *Gender Differences in Age Among Psychiatric Residents*

As shown in table 2, in 1986 the largest proportions of female physicians and psychiatrists were found in the group less than 35 years old: 25% of the physicians and 35% of the psychiatrists in this age group were women. These percentages were higher than those for any other age group, indicating that the increase in the proportion of women in medicine is due primarily to the number of women younger than 35. As reported by AMA (9), 4,968 women represented 31% of all graduates of U.S. medical schools in 1986, but women represented only 27% of all medical residents under age 35 in 1986.

A study of 141 female and 114 male psychiatrists who had been in training in 1974 (10) showed that there was a significantly greater interval between grad-

**TABLE 3. Number of Physicians and Female Physicians in Selected Specialties, 1970–1985**[a]

| | 1970 | | 1975 | | 1980 | | 1985 | | % Change, 1970–1985 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Specialty | Women | Total | Women | Total | Women | Total | Women | Total | Women | Total |
| Psychiatry[b] | 2,942 | 23,236 | 3,803 | 26,503 | 5,257 | 30,752 | 7,732 | 36,038 | 162.8 | 55.1 |
| Anesthesiology | 1,516 | 10,860 | 1,819 | 12,861 | 2,388 | 15,958 | 3,710 | 22,021 | 144.7 | 102.8 |
| General practice[c] | 2,486 | 57,948 | 2,866 | 42,374 | 4,677 | 32,519 | 7,996 | 27,030 | 221.6 | −53.4 |
| General surgery | 311 | 29,761 | 567 | 31,562 | 1,150 | 34,034 | 1,987 | 38,169 | 538.9 | 28.3 |
| Internal medicine | 2,383 | 41,872 | 4,006 | 54,331 | 8,130 | 71,531 | 14,716 | 90,417 | 517.5 | 115.9 |
| Obstetrics/gynecology | 1,337 | 18,876 | 1,777 | 21,731 | 3,243 | 26,305 | 5,597 | 30,867 | 318.6 | 63.5 |
| Pathology | 1,273 | 10,283 | 1,674 | 11,720 | 2,215 | 13,402 | 3,217 | 15,456 | 152.7 | 50.3 |
| Pediatrics | 3,751 | 17,941 | 5,081 | 21,746 | 8,117 | 28,342 | 12,373 | 35,617 | 229.9 | 98.5 |
| All physicians | 25,401 | 334,028 | 35,636 | 393,742 | 54,284 | 467,679 | 80,725 | 552,716 | 217.8 | 65.5 |

[a] Data are from the AMA (8).
[b] Includes child psychiatry.
[c] Includes family practice.

**TABLE 4. APA Age Groups of All Psychiatric Residents and Female Psychiatric Residents, Academic Years 1983–1987**[a]

| | 1983–1984 | | | 1984–1985 | | | 1985–1986 | | | 1986–1987 | | | 1987–1988 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age Group | All | Female | | All | Female | | All | Female | | All | Female | | All | Female | |
| (years) | Residents | N | % | Residents | N | % | Residents | N | % | Residents | N | % | Residents | N | % |
| 20–29 | 2,004 | 700 | 34.9 | 1,960 | 700 | 35.7 | 1,886 | 696 | 36.9 | 1,761 | 671 | 38.1 | 1,854 | 732 | 39.5 |
| 30–39 | 2,416 | 906 | 37.5 | 2,613 | 988 | 37.8 | 2,803 | 1,122 | 40.0 | 2,907 | 1,206 | 41.5 | 3,041 | 1,252 | 41.2 |
| 40–49 | 421 | 206 | 48.9 | 377 | 175 | 46.4 | 374 | 155 | 41.4 | 414 | 187 | 45.2 | 435 | 213 | 49.0 |
| 50–59 | 102 | 40 | 39.2 | 108 | 41 | 38.0 | 85 | 36 | 42.4 | 78 | 34 | 43.6 | 82 | 31 | 37.8 |
| 60 and older | 15 | 4 | 26.7 | 13 | 1 | 7.7 | 9 | 1 | 11.1 | 4 | 0 | 0.0 | 6 | 1 | 16.7 |
| Age not reported | 151 | 58 | 38.4 | 237 | 91 | 38.4 | 323 | 123 | 38.1 | 334 | 143 | 42.8 | 397 | 173 | 43.6 |
| Total | 5,109 | 1,914 | 37.5 | 5,308 | 1,996 | 37.6 | 5,480 | 2,133 | 38.9 | 5,498 | 2,241 | 40.8 | 5,815 | 2,402 | 41.3 |

[a] Data are from the APA census of residents. Percents based on total number of psychiatric residents for whom age was reported.

uation from medical school and beginning of psychiatric residency training for women than for men. The interval, measured in number of years, yielded a mean of 4.65±6.72 years for women and 2.78±4.50 for men ($t=2.53$, $df=252$, $p<0.01$). In addition, the mean±SD ages of men and women were essentially identical at graduation from medical school, 26.5±3.4 for women and 26.3±2.1 for men ($t=0.47$, $df=252$, $p=0.640$). However, at the beginning of psychiatric residency training, the difference between the sexes in mean age, 31.1±6.7 for women and 29.1±4.9 for men, was statistically significant ($t=2.67$, $df=252$, $p<0.01$). These findings would seem to indicate that female residents more often begin specialty training later in life than do their male counterparts (perhaps because of children and/or other family obligations), take more time to complete residency, or choose psychiatry after training in other specialties.

The APA data given in table 4 support this pattern for psychiatric residents over the period from 1983–1984 to 1987–1988. The percentages of women over these years was consistently and substantially higher in the 40–49-year-old age group than in the 20–29-year-old or 30–39-year-old groups. The proportion of female psychiatric residents has remained stable at 49% in the 40–49-year-old age group between 1983–1984 and 1987–1988, but there have been substantial increases in the proportion of women in the younger groups. Between 1983–1984 and 1987–1988, the proportion of female psychiatric residents rose from 35% to 40% in the 20–29-year-old group, and both the percentage and the number of female psychiatric residents increased in the 30–39-year-old age group. Although the mean age of psychiatric residents has remained fairly stable over this time period, in 1983–1984 the mean age of male psychiatric residents was 31.9 and that for female psychiatric residents was 32.6; in 1987–1988, the mean ages were 32.3 and 32.5, respectively. These findings suggest that the relatively lengthy interval for women between graduation from medical school and beginning of psychiatric residency training may no longer be as common as it was a decade ago.

## CONCLUSIONS

The AMA (11) reported that between 1970 and 1986 the percentage of male physicians in the United States increased by 52% while that of female physicians increased by 262%. Projections for the year 2000 also indicate a disproportionate increase in the number of female physicians compared with their male counterparts. Based on a "best projection" model that includes predictions about how the production of new physicians is most likely to change between 1986 and 2000, AMA projected that there will be a 92% increase in the number of female physicians, compared with a 9% increase in the number of male physicians.

If the number of female physicians continues to grow as predicted, and even if women more often choose specialties previously dominated by men, there is no reason to believe that the high representation of women in the field of psychiatry will change. In an analysis of specialty choice based on 1978–1986 specialty transitions of the group of residents who began residency training in 1978, AMA (11) reported that female physicians were much more likely than male physicians to practice in pediatrics, obstetrics/gynecology, and psychiatry. Consequences of the increased number of women have already been felt in psychiatric residency training programs. As reported in the September 1988 newsletter of the American Association of Directors of Psychiatric Residency Training (12), training programs are addressing issues particularly important to female residents, such as the structure of the program (pregnancy/parental leave policies, part-time residency and related time conflicts, and personal safety), curriculum content (the effects of the sex of the therapist and pregnancy on transference and countertransference issues and negative diagnostic stereotypes for female patients), and career choices and advancement opportunities for female psychiatrists (effects of early socialization on women, lack of time due to multiple roles, entry into research programs, and scarcity of mentors and/or role models).

Studies have demonstrated that female psychiatrists are less often Board certified, earn lower incomes, work fewer hours per week, and tend to work in institutional settings (13). As reported by Weinstein in 1967 (14), Arnhoff and Kumbar in 1973 (15), and Roback et al. in 1987 (6), the percentage of women who are Board certified in psychiatry is consistently lower than the percentage of men who are so certified. Robinowitz et al. (16) reported that women in academic medical positions are more likely to be given less prestigious assignments and that they are underrepresented in administrative and leadership positions.

Similarly, Fenton et al. (17) demonstrated that female psychiatrists spend a greater proportion of their time in organized settings and are less involved in academia or private practice, that they tend to see a greater number of female patients, and that they see their patients more frequently, a finding that also holds for female practitioners in family practice and internal medicine.

Narrative examples suggest that these differences may be changing as more women enter specialties previously dominated by men because these women may take on male practice characteristics, at least with respect to location and mean number of hours worked per week. Even though gender differences in some practice characteristics may be disappearing, other, more positive differences may have a beneficial impact on the quality of patient care. Maheux et al. (18) reported persisting attitudinal differences in a study involving general practitioners in Quebec. These authors noted that women represent 44% of the medical school enrollees in all of Canada, but in French Canadian medical schools women represented 58% of the student population in 1987–1988. Maheux et al. found that female caregivers were more likely to value psychosocial factors in patient care, to educate patients about their health problems, and to counsel patients about health matters, suggesting that female physicians have more social concerns and that they show a greater orientation toward patients in their practice than their male counterparts. The authors also concluded that neither medical training nor the organization of medical practice succeeds in eliminating these attitudinal differences. It is conceivable that these female values and interests would also influence the research questions and funding of the future, leading to a greater emphasis on prevention and health maintenance. The growing number of women in medical specialties can be seen as having great potential for important contributions to the quality of patient care.

If women in medicine are succeeding in contributing to the quality of health care services provided, in increasing the availability of quality child care, in eliminating salary inequalities, and in promoting more flexible work schedules, the area of access to leadership roles is still an important challenge. Numerical dominance alone is not sufficient to ensure leadership. As Constanza (19) noted, the status of female physicians in England and the Soviet Union has not increased as a function of their increased numbers. Constanza proposed that some attributes of leadership would have to change (for example, aggressiveness and competitiveness would have to be deemphasized) and that medical leadership must become gender neutral by incorporating female values and strengths.

Although the data suggest some potential leveling off in the percentage of women entering psychiatric residency training, we are seeing a considerable increase in both the number and the proportion of women in practice. There is concern among some leaders that the influx of women reflects (or contributes to) lowered prestige and value in the specialty. Given the decrease in stigma related to psychiatric diagnoses, increases in access to care, and the advances in diagnosis and treatment, such an explanation seems unlikely although worthy of attention. Increased access to leadership roles for female psychiatrists will provide much needed role models as well as changes in focus on the values and strengths associated with quality patient care. Thus, the growth and trends in resident demographics and content must be monitored closely to predict and adapt to further changes in the field and to meet patient care and research needs.

# Criminalization of Psychotherapist-Patient Sex

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*Legislative enactment of criminal penalties for psychotherapists' sexual contact with their patients is pending in several states. The arguments in favor of criminalization are that it serves as a deterrent, offers retribution, provides redress when other avenues are blocked, deals with unlicensed psychotherapists, makes victims' assistance funds available, and provides due process protection against false accusations. In opposition to criminalization are the arguments that civil and administrative measures already exist to deal with the problem, it may have a chilling effect on the reporting of misconduct, it may void malpractice insurance, it makes guilty psychotherapists place themselves in jeopardy if they acknowledge their wrongdoing in attempting to make amends, it removes control of the legal process from the victim, it fails to offer rehabilitation, and it singles out psychotherapists from other fiduciaries for more stringent treatment. APA district branches inevitably will be called on to take positions with regard to legislation criminalizing sexual exploitation of patients. The current public outrage over patient victimization, however appropriate it may be, appears to make it difficult to publicly justify anything other than support for criminalization.*

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Over the past 15 years the public has become increasingly aware of the issue of psychotherapist-patient sexual contact. Newspapers report civil damage awards to sexually exploited patients amounting to millions of dollars, as well as revocation or suspension of the offending practitioners' licenses by licensing boards. Psychotherapists themselves—psychiatrists, psychoanalysts, psychologists, and social workers—have focused with increasing intensity on the issue, as evidenced by a burgeoning literature (1, pp. 575–614). We have attempted to address this problem through professional education and by declaring that sexual relations with patients are unethical and that sexual relations with former patients are almost always unethical (2).

Some critics regard the profession's response as inadequate given the scope of the problem. Nationwide studies have revealed that somewhere between 7% and 15% of psychotherapists engage in sexual contact with their patients and that over 90% of the victims suffer harm (3–5). Notwithstanding the educational efforts of professional groups and the substantial risks to clinicians engaging in sexual relations with patients, reports of the behavior continue to surface. The public has demanded punitive action. Coalitions of victims, patients' rights groups, and concerned professionals have pressured state legislatures to enact statutes making psychotherapist-patient sex a criminal offense.

Legislators will be looking to professional societies, such as APA district branches, for guidance and advice as they attempt to draft such laws. Before an informed judgment about criminalization can be made, the issues surrounding it must be carefully considered. In this paper we will attempt to clarify those issues by presenting the arguments for and against criminalization.

## OVERVIEW OF CRIMINALIZATION

The first call for criminalization came from Masters and Johnson in 1975 (6). To date, seven states have passed such statutes and other legislatures are considering them (7). In 1983 Wisconsin became the first state to enact a statute making psychotherapist-patient sexual exploitation a criminal offense (8). Minnesota (9), North Dakota (10), and Colorado (11) soon followed. Such statutes were adopted by California (12) and Maine (13) in 1989 and by Florida in 1990 (14). Currently, the legislatures of Iowa, Maryland, Massachusetts, New Mexico, and Pennsylvania are considering similar bills. Although seven states have criminalized the conduct, the issue is far from settled. Criminalization is a complex and controversial matter. There are a number of clinical, ethical, and legal considerations to be weighed in deciding its appropriateness as social policy.

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## ARGUMENTS FOR CRIMINALIZATION

### *Deterrence*

Deterrence is the primary argument in favor of criminalization of psychotherapist-patient sexual activity. A criminal law articulates to everyone the wrongfulness of such behavior. Proponents believe that sexual contact would be restrained by an unmistakable legal message that such behavior is severely damaging and totally unconscionable backed by the threat of a felony conviction and a prison sentence. Controversy exists over the probable effectiveness of this deterrence, but among the categories of exploitative therapists (1, p. 402; 15), those who are naive, uninformed, or undergoing the effects of midlife crisis may well respond to the prospect of punishment.

### *Retribution*

In addition to the utilitarian function of deterrence, retribution is also a primary goal of criminal statutes. Whereas retribution originally derived from private, personal vengeance, under the "just desserts" theory the state responds to a violation of its rules with punishment for its own sake (16). This morally justified retaliation constitutes a vindictive justice that metes out suffering to pay back the wrongdoers. One of the strongest arguments for criminalization may now be that sexual exploitation, in the light of the evidence documenting its ill effects on patients, is so outrageous a transgression of societal rules that retribution is called for. Although therapist behavior rooted in the character pathology of impulsive, narcissistic, or sociopathic personalities may not be deterred by criminalization, retribution for such individuals may nonetheless be socially appropriate.

### *Additional Redress*

A criminal statute would augment existing procedures that, for one reason or another, have not functioned effectively. In the past, an exploited victim could obtain redress for sexual exploitation only through complaints to professional societies' ethics committees, complaints to licensing authorities, or lawsuits for civil damages. Each of these routes has presented problems. Ethical procedures are ponderous, often involving long delays and ineffective action from the professional societies, themselves fearful of being sued by therapists. Licensing authorities have often been unresponsive or impotent. A civil lawsuit can be very expensive and may drag on for years. Criminalization, then, provides an additional option for a victim when other avenues fail. Implementing this option, however, may itself be lengthy and be delayed by the motions of a defendant exercising due process rights.

### *Dealing With Unlicensed Therapists*

Although no panacea, criminalization may also provide a practical way to deal with unlicensed therapists and to incapacitate practitioners who continue to practice unregulated after their licenses have been revoked (17). Licensure boards cannot sanction them, and many of them have so few financial resources that a civil suit would be fruitless. A weakness of the criminal process, however, has been demonstrated in Minnesota, where the relatively short sentences imposed on convicted therapists have allowed them to return to practice after brief incarcerations. A proposal before the Massachusetts legislature may provide a more constructive solution. This law would allow a court to issue an injunction against the unlicensed practice of psychotherapy by a therapist who has had sexual contact with patients. Breach of the injunction would subject the offender to criminal contempt procedures.

### *Money to Treat Victims*

Proponents of criminalization point out that such laws can provide access to money for both prevention and treatment of victims. Minnesota, for example, has used money from federal criminal justice programs to fund educational efforts dealing with the problem (18). Money may be available to help fund ongoing victim treatment in states where public funds are dedicated to assistance of crime victims. Such financial restitution, however, may represent an unkept promise. Although funds for assistance to crime victims do exist in theory, the current austerity of state budgets has led to large cuts in the funding of such programs.

## ARGUMENTS AGAINST CRIMINALIZATION

### *Obscuring the Issue*

Paradoxically, criminalization may cause psychotherapist-patient sex to be reported even less. Colleagues may be less willing than they currently are to report an offending psychotherapist if an ethics complaint would lead to criminal charges. This might be the case despite an ethical duty to report (2) and the statutes on mandatory reporting that some states have passed (19). A patient may also be reluctant to complain, appalled at the idea that the psychotherapist would be subject to criminal sanctions. While some complainants want retribution or restitution, others may want help for their impaired therapists. Although some patients may not be aware of it, criminal prosecutions cannot proceed without their testimony, which they can choose to withhold.

### *Voiding Malpractice Coverage*

One of the gravest concerns of victims of therapist exploitation is that criminalization may void malpractice insurance coverage. Although insurers continue to recognize an obligation to defend accused therapists, the trend has been to exclude paying judgments for sexual exploitation. Criminalization provides additional justification for such exclusion, as most policies specifically exclude criminal acts from coverage. Criminalization, then, may eliminate a resource that victims sorely need to finance continuing treatment. There is no victim compensation fund comparable to the therapist's malpractice policy. Although the victim may be able to reach the personal assets of the psychotherapist, these resources are frequently inadequate or nonexistent.

This concern about loss of malpractice coverage may be exaggerated. There are indications that insurers may be required to indemnify such claims even in states which have criminalizing statutes (20). Successful suits are frequently based on assertions of mishandled transference. One appellate opinion has held that in such circumstances, "It is the mishandling of transference, and not the resulting sexual conduct, which gives rise to the alleged malpractice.... The sexual acts are an incidental outgrowth of the primary malpractice, not the proximate cause" (21). Some plaintiffs have won lawsuits despite these exclusionary policies by alleging concurrent proximate causes for their injuries—where the injuries have been caused by both the excluded risk (sexual misconduct) and an insured risk (such as wrongful or improper termination of therapy).

### *Impairment of Civil Actions*

Criminalization may make it more difficult for patients to win civil suits for damages. The risk of criminal prosecution certainly will make offending therapists less likely to admit their behavior. The therapist may exercise Fifth Amendment rights. This in effect will prevent the process of discovery by civil and administrative boards until the criminal trial is completed. This could delay not only an award of (money) damages but also restriction or revocation of the therapist's license by the licensing board. Even the simple matter of apology, which some victims find healing, becomes difficult in the face of a possible criminal prosecution. Thus the "malignant synergy of a bad outcome . . . and bad feelings—patient guilt, grief, rage, surprise, and abandonment" (22) is almost assured.

### *Inappropriate Catharsis*

Victims' advocates observe that pursuit of criminal prosecution provides an anodyne to the shame and feelings of powerlessness experienced by victims of sexual exploitation. Whether this emotional relief is greater than that obtained through a civil lawsuit or action before a licensing board is unclear. Nevertheless, it may be inappropriate to use the blunt instrument of criminal law to palliate and enable victims. Desirable as these goals may be, they do not fall within the traditional purposes of criminal law: retribution, deterrence, incapacitation, and rehabilitation of offenders.

### *Loss of Control of Process*

Many victims of sexual exploitation by psychotherapists feel that they have lost control of their lives, and involvement in criminal prosecution may heighten this feeling. Although some writers believe that a decision to file a criminal complaint helps recover a sense of control, the victim does not control a criminal process and civil process in the same way. Although the victim is free to choose whether or not to come forward with a complaint and a prosecutor cannot proceed if the only witness against the therapist refuses to testify, victims have been concerned that after a complaint is entered the prosecutor's decisions will determine how the case is run.

### *Unproven Deterrence*

Although anecdotal information and common sense suggest that criminalization may act as a deterrent, there is as yet no empirical evidence to demonstrate this premise. In fact, few people even file criminal charges in states where statutes exist. Over 1,600 victims of therapist sexual contact have been seen in the Walk-In Counseling Center in Minneapolis, but Minnesota has prosecuted only nine criminal charges to date.

### *Absence of Rehabilitation*

The absence of a provision for the rehabilitation of offenders is a major omission in the current criminal statutes. Although some sexual exploiters victimize multiple patients, appear to be without conscience, and are probably not treatable, others commit a single offense that may be a response to a situational or life cycle crisis, and these psychotherapists might benefit from treatment and be restored to social productivity. Casting these latter individuals in the role of unredeemable criminals may not be wise social policy.

## SPECIAL CONSIDERATIONS

### *Consent*

Some criminal laws, such as those against rape and indecent assault, already apply to therapist sexual misconduct. As a practical matter these laws cover only the most egregious cases, and consent of the victim is an absolute defense (17). Eliminating consent as an issue by defining psychotherapist-patient sexual contact as a specific crime provides a more effective statute. Most statutes criminalizing patient-therapist sex exclude consent as a defense, defining such contact as a crime regardless of the victim's behavior. This strict liability standard means that the only matter to be adjudicated is whether the sexual contact occurred.

Some commentators believe that removing the defense of consent in effect portrays psychotherapy patients as incompetent "presumptive sillies"(23). If this were to occur, the status of patients would clearly be stigmatized. As a practical matter, in our experience victims are not concerned that they will be demeaned through the removal of the issue of consent. Obviously, competent adults are presumed capable of consent and the law is reluctant to remove this presumption. Drawing an analogy between psychotherapy patients and rape victims, as in Masters and Johnson's original proposal, appears to infantilize them by saying that patients are ipso facto unable to consent. This, however, is not the best way to conceptualize the issue.

It is not that the victim cannot consent or that consent is improperly obtained—as through undue influence of transference or lack of information about risks. Consent is irrelevant. The issue is fiduciary breach and abuse of power in the therapeutic relationship. A fiduciary is in a position of special trust, analogous to that of a trustee, involving "a duty to act primarily for another's benefit" and requiring "scrupulous good faith and candor" (24). Trust and confidence are reposed in the therapist on the basis of a perception of social role. Even a sophisticated patient must place himself or herself in a vulnerable, less powerful position vis-à-vis a therapist who has more knowledge, training, and experience of the therapeutic process. It is the duty of the therapist as fiduciary to attend only to the needs of the patient and to do no harm. Sexual contact is countertherapeutic behavior that will harm patients. The consequences of such acts are so socially deleterious that they call for proscription regardless of consent. Attention should focus entirely on the therapist's behavior, not on that of the victim.

### *Additional Burdens*

Criminalization adds what may appear to be an unreasonable layer of special requirements to the civic liabilities of mental health personnel, in a manner similar to the effects of the *Tarasoff* decision. Some believe that it is simply unfair to criminalize the breach of one type of fiduciary relationship while ignoring sexual breaches of other types of fiduciary relationships, such as teacher-student, attorney-client, guardian-ward, and trustee-beneficiary (25). On the other hand, perhaps the law should deal more sternly with those exploitations of positions of special trust; we do have laws against insider trading of securities.

### *False Accusations*

For psychotherapists the possibility of having to defend themselves against false accusations of sexual misconduct is terrifying, and false accusations do occur (26). The criminal law, although it exposes the accused therapist to greater jeopardy, provides better protection against false accusations of sexual exploitation than the civil law. The standard of proof in a criminal trial is "beyond reasonable doubt," whereas in a civil trial a jury can find for the plaintiff on "the preponderance of the evidence." In an ambiguous situation a properly instructed criminal court jury should be less likely to enter a judgment against a therapist than a jury in a civil trial. In actuality the difficulty of proving a criminal case beyond reasonable doubt may make prosecutors hesitant to proceed. The vast majority of these cases involve alleged actions in an office in which only two people were present, and the evidence is limited to one person's word against another's. The narrow and specific definition of behavior in a criminal statute, which is necessary to avoid constitutional challenge of the statute on the basis of vagueness, means that a therapist may avoid criminal conviction for acts that could incur civil liability. The criminal law also offers more due process protection to the accused therapist than proceedings before licensure boards, which may allow testimony that would be excluded under strict rules of evidence and which may not be governed by a statute of limitations.

## CONCLUSIONS

APA district branches inevitably will be called on to take positions with regard to legislation criminalizing sexual exploitation of patients. The current political climate of public outrage over patient victimization, however appropriate it may be, appears to make it difficult to publicly justify anything other than support for criminalization. Awareness of the drawbacks of such legislation may be useful in the deliberations.

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## New Policy for References

Effective with the September 1991 issue, *The American Journal of Psychiatry* will institute a policy of listing the names of all authors of work cited in references. Authors of submitted manuscripts and letters to the Editor must include the surnames and initials of all authors in references. The use of "et al." is no longer acceptable.

# Object Representations in the Early Memories of Sexually Abused Borderline Patients

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*Objective: This study analyzed psychological representations in 58 subjects in order to achieve a better understanding of the relation between adult borderline personality disorder and reported histories of childhood sexual and physical abuse. Method: The subjects were 29 inpatients with borderline personality disorder diagnosed according to the Diagnostic Interview for Borderlines, 14 nonborderline inpatients with major depressive disorder according to the Research Diagnostic Criteria, and 15 normal comparison subjects recruited from the community and screened for the absence of psychopathology. Earliest memories were used as the source of mental representations in all subjects. The memories were reliably coded for malevolent affect tone, presence of deliberate injury, and effectiveness of helpers. Family histories of childhood sexual and physical abuse were obtained with the Familial Experiences Interview, a structured interview. Abuse histories for a subset of the subjects were corroborated by interviews with family members. Results: A reported history of sexual abuse, but not a reported history of physical abuse, predicted the presence of extremely malevolent representations in these earliest memories as well as representations involving deliberate injury. These two kinds of representations also discriminated borderline patients who reported histories of sexual abuse from borderline patients who did not report sexual abuse. Mean affect tone (from malevolent to benevolent) did not, however, discriminate sexually abused or physically abused subjects. Conclusions: The results suggest that malevolent representations associated with the borderline diagnosis in previous research may be partially related to a history of childhood sexual abuse. Implications for the object relations theory of borderline personality disorder are noted.*

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Psychodynamic theory states that patients with borderline personality disorder suffer from pathological object relations (1, 2). While the term "object relations" sometimes refers to actual interpersonal relations, difficulties in external relations are thought to be a reflection of difficulties in the internal "object world." Internal mental representations of the self and others, as well as affects and expectations attached to them, are referred to as object representations (3, 4). Because of the theoretical importance of object relations for psychodynamic understanding of borderline personality and because of growing evidence of an association between borderline personality disorder and a history of childhood trauma (5–10), we examined the relation between borderline patients' object representations and childhood sexual abuse.

Empirical attempts to appreciate developmental problems that could account for borderline patients' disturbed object relations led researchers to study the early familial experiences of these subjects. A high prevalence of reported childhood trauma, particularly sexual abuse, was found (5–10). Zanarini et al. (5), Ogata et al. (6), Links et al. (7), and Herman et al. (8) found that sexual abuse and sometimes physical abuse discriminated borderline patients from patients with other axis II disorders, major depression, borderline traits, and bipolar II disorders, respectively. Both sexual abuse and physical abuse have been found to discriminate adolescent psychiatric inpatients with borderline personality disorder from those without the

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disorder (9, 10). Survey studies suggest that the prevalence of a history of sexual abuse may be as high as 57% among psychiatric inpatients and 33% among nonclinical populations (11–13) and that the abuse occurs across economic classes and ethnic groups (13–15).

Adult sequelae of childhood sexual abuse are similar to some clinical features of borderline personality disorder. Long-term sequelae include poor impulse control, self-blame, suicidal behavior, poor self-esteem, substance abuse, sexual problems, lack of trust in interpersonal relations, depression, and self-destructive behavior such as biting, cutting, and burning (16–19).

No published research has explored, however, the association between the traumatic histories found among borderline patients and specific aspects of borderline object representations. Childhood abuse could contribute to borderline pathology through impaired development of object relations.

This study assessed object representations with the Early Memories Test. The test in various forms has been used by psychodynamically oriented clinicians and researchers and others for clinical assessment of object relations (20–23) and may reflect stable characteristics of personality (24, 25).

We examined the association between reported history of sexual abuse and affective quality of object representations as determined from the following aspects of the Early Memories Test: 1) accounts involving deliberate injury, 2) effectiveness of helpers in accounts in which injury or illness occurred, 3) affect tone (from malevolent to caring) in the relationships portrayed in the accounts, and 4) accounts that portrayed extremely malevolent interactions. We chose variables associated with the affective quality of relationships because previous studies have suggested that borderline patients are discriminated from patients in other diagnostic groups by their malevolent internal object world (26–29). We hypothesized that sexually abused subjects would report earliest memories in which others were more injuring, less helpful, and more malevolent. In addition to studying the association of responses on the Early Memories Test with sexual abuse among borderline patients, we also studied this association among patients with major depressive disorder and among normal subjects. The patients with major depression were part of an ongoing study of the relation between borderline patients and subjects with affective disorders (30, 31).

## METHOD

Male and female inpatients between the ages of 18 and 60 years who fulfilled at least two of the *DSM-III* criteria for borderline personality disorder or schizotypal personality disorder or three of the criteria for a major depressive episode were potential subjects. Before being included, potential subjects were assessed as described below. Exclusion criteria included organic disorders, chronic psychosis, age over 60, English not the native language, and IQ below 65.

Eighty-seven percent of the 50 eligible patient subjects gave written consent to take part in this study. While drug free they were administered the Diagnostic Interview for Borderlines (DIB) (32) by a research team member. Our group's interrater reliability (kappa=0.80) for the DIB has been established (33) and is maintained through periodic retraining. Patients who scored more than 7 on the DIB entered the borderline group. Those who scored less than 5 on the DIB and who met the Research Diagnostic Criteria (RDC) (34) for major depressive disorder were the nonborderline depressed comparison subjects. RDC diagnoses of depression were reliably made by senior supervisors who were also research group members (weighted kappa [35]=0.92) in conjunction with the patients' primary therapists; both the supervisor and the therapist were blind to the subjects' DIB result. Subjects scoring 6 on the DIB were excluded in advance to minimize group overlap. These cutoffs provide optimal balance between DIB sensitivity and specificity (36).

Normal subjects were recruited through public advertisements requesting volunteers "in good physical and emotional health who have never been in psychotherapy and are reasonably content with their lives." The screening procedure has been described elsewhere (26). All normal subjects scored less than 5 on the DIB. All gave written consent.

The total number of subjects in the three study groups was 58. There were 29 patients with borderline personality disorder, 14 depressed patients, and 15 normal subjects.

Researchers blind to DIB and RDC results interviewed all subjects regarding a variety of early familial events, including childhood physical and sexual abuse. The Familial Experiences Interview was developed by Ogata in collaboration with our research team (6). The areas explored include losses, separations, illnesses, school problems, abuse, neglect, and other events. The question sequence was the same for all subjects. Sexual abuse was defined as exposure to genitals with no physical contact, fondling or caressing of genitals, or penetration; all but one of the incidents of reported sexual abuse consisted of fondling or penetration. Physical abuse was defined at minimum as striking the head or body, excluding spanking. Interrater reliabilities for the interview items reported in this article ranged from 0.75 to 1.00 (weighted kappa) for three raters. Administrators of the interview were blind to the subjects' diagnoses and Early Memories Test results.

Subjects were given a psychological test battery that included a modified version of Mayman's Early Memories Test (20, 21). They were asked to relate their earliest memory and the next earliest memory, their earliest memory of mother and earliest memory of father, their most happy and most unhappy memory, their earliest memory of feeling scared, angry, snug/cozy, excited, and ashamed or guilty, and their favorite early memory.

The typed verbatim early memories were sorted by kind of memory (so that a subject's response to one prompt would not influence rater scoring of subsequent responses) and coded by two raters independently. Consensus was obtained on discrepant scores. Only earliest and next earliest memories and earliest memory of mother and of father are included in this report, since these prompts are affectively neutral.

Deliberate injury was scored as present whenever an early memory included intentional attack or assault with physical contact, including pushing, shoving, or hitting. Memories were not scored positive for emotional injury or threat if there was no physical contact. Sexual assaults portrayed in the Earliest Memories Test were coded separately and were not counted as memories of injury for this study, so as to avoid confounding dependent and independent variables. Injuries were scored yes/no (kappa=0.95). The following were scored as containing a deliberate injury:

> My earliest? I remember when I was . . . going to school and I was pushed around by this girl and her gang at school. I mean, she physically pushed me around . . . . I kind of, I was always picked on.

> First day of kindergarten . . . running out of the classroom and being stopped at the end of the hallway by the superintendent. I remember him pushing me down on the bench and hitting my head on the wall, and crying, and my brother came from another classroom to help, and the superintendent made him go back into his classroom.

The effectiveness of helpers was coded on a 5-point ordinal scale (reliability=0.83, weighted kappa): 1= no helper present, 2=helper present but made no attempt to help or was oblivious to problem; 3=helper attempted to intervene but was ineffective; 4=helper provided partial relief, comfort, or protection; 5= helper provided complete relief, recovery, or protection. Helper effectiveness was rated only when there was illness or accidental or deliberate injury present in an Earliest Memories Test response.

Finally, each memory was assigned a global score for affect tone by using a 5-point continuous scale devised by Westen and Barends (37) (reliability by uncorrected intraclass correlation coefficient, 0.78; with Spearman-Brown correction, 0.88). The scale measures the "affective quality of representations of people and relationships, or interpersonal expectancies portrayed, from malevolent to benevolent": 1=unambivalent, profound, overwhelming malevolent representations; people are seen as randomly capricious and destructive; 2=hostile, empty, or capricious representations but not profoundly malevolent and not overwhelming; people may be unpleasant but are not seen as threats to one's existence; 3=a range of mixed representations with a mildly negative tone; people are seen as capable of caring and being cared for; 4=a range of mixed representations with a neutral or mildly positive tone; people are generally seen as being cared for and enjoying one another's company; 5= predominantly positive, benign, and caring representations; intimacy, love, and loyalty can be generally expected.

**TABLE 1. Characteristics of Borderline and Depressed Patients and Normal Subjects in a Study of Earliest Memories**

| | Borderline Patients (N=29) | | Depressed Patients (N=14) | | Normal Subjects (N=15) | |
|---|---|---|---|---|---|---|
| Characteristic | N | % | N | % | N | % |
| Female sex | 23 | 79 | 9 | 64 | 9 | 60 |
| Caucasian race | 26 | 90 | 14 | 100 | 15 | 100 |
| Married | 4 | 14 | 9 | 64 | 6 | 40 |
| Divorced/separated | 7 | 24 | 1 | 7 | 3 | 20 |
| Never married | 18 | 62 | 4 | 29 | 6 | 40 |
| Report of childhood sexual abuse[a] | 21 | 72 | 4 | 29 | 3 | 20 |
| Report of childhood physical abuse | 14 | 48 | 6 | 43 | 3 | 20 |

[a] Significant difference between groups ($\chi^2$=13.76, df=2, p<0.01).

For the Earliest Memories Test, injury responses were analyzed by chi-square and ratings of the effectiveness of helpers by analysis of variance (ANOVA). Affect tone scores were first analyzed as continuous data by ANOVA. The presence or absence of extreme malevolence was then treated as categorical and analyzed by chi-square. To test for possible confounding data, we performed logistic regression and multiple regression analyses.

## RESULTS

Table 1 shows the composition of the sample of 58 subjects. Twenty-four (83%) of the 29 patients who were borderline patients according to the DIB met the *DSM-III* criteria for borderline personality disorder, and seven of the 24 also met the *DSM-III* criteria for schizotypal personality disorder. The subjects were predominantly female and Caucasian. The borderline patients were significantly younger (mean±SD age for borderline patients, 30.3±8.6 years; for depressed patients, 41.8±9.5 years; for normal subjects, 37.1± 11.0 years; F=7.53, df=2, 55, p=0.001). The borderline patients also had a significantly lower average socioeconomic status (mean±SD for borderline patients [N=26], 36.6±13.2; for depressed patients [N= 12], 47.3±11.5; for normal subjects [N=13], 51.4± 9.0; F=7.70, df=2, 48, p=0.001). Borderline subjects reported significantly more childhood sexual abuse. The average age at onset of abuse was 6–8 years. Rates of reported physical abuse did not differ significantly among the three groups.

Deliberate injury responses on the Earliest Memories Test were significantly more frequent among subjects who reported histories of sexual abuse (table 2). Deliberate injury also discriminated borderline patients who reported sexual abuse from those who did not. All subjects with test responses containing reports

**TABLE 2. Relation Between Deliberate Injury in Four Earliest Memories[a] and Reports of Childhood Sexual Abuse in Borderline and Depressed Patients and Normal Subjects**

| | Injury in Early Memory | | |
|---|---|---|---|
| Group | Yes | No | Fisher's p |
| All subjects (N=58) | | | 0.0001 |
| Abused (N=28) | 11 | 17 | |
| Nonabused (N=30) | 0 | 30 | |
| Borderline and depressed patients (N=43) | | | 0.001 |
| Abused (N=25) | 11 | 14 | |
| Nonabused (N=18) | 0 | 18 | |
| Borderline patients only (N=29) | | | 0.03 |
| Abused (N=21) | 9 | 12 | |
| Nonbused (N=8) | 0 | 8 | |

[a] Earliest memory, next earliest memory, earliest memory of mother, and earliest memory of father.

**TABLE 3. Relation Between Affect Tone of Four Earliest Memories[a] and Reports of Childhood Sexual Abuse in Borderline and Depressed Patients and Normal Subjects**

| | Affect Tone Score[b] | | Significance[c] | | |
|---|---|---|---|---|---|
| Group | Mean | SD | t | df | p |
| All subjects (N=58) | | | 2.75 | 54 | 0.01 |
| Abused (N=28) | 2.76 | 0.98 | | | |
| Nonabused (N=30) | 3.27 | 0.44 | | | |
| Borderline and depressed patients (N=43) | | | 1.97 | 40 | 0.08 |
| Abused (N=25) | 2.69 | 0.95 | | | |
| Nonabused (N=18) | 3.17 | 0.46 | | | |
| Borderline patients only (N=29) | | | 1.29 | 26 | n.s. |
| Abused (N=21) | 2.55 | 0.93 | | | |
| Nonabused (N=8) | 3.00 | 0.46 | | | |

[a] Earliest memory, next earliest memory, earliest memory of mother, and earliest memory of father.

[b] Higher score=more benevolent affect; scale of 1–5.

[c] One-tailed, with Bonferroni correction.

of deliberate injury also reported childhood sexual abuse. In a secondary analysis we found that accounts of sexual assault in the first four Earliest Memories Test responses occurred for only three subjects, all of them sexually abused borderline subjects. Of these three, two had not received a score for deliberate injury on the first four memories.

To test for possible confounding data, we performed logistic regression analyses. Demographic differences were tested first by likelihood ratio chi-square to determine whether they had sufficient predictive power to warrant controlling for them. Only age predicted deliberate injury responses on the Earliest Memories Test ($\chi^2$=5.07, df=1, p=0.02). Socioeconomic status did not and was excluded. A model that included age, diagnosis, physical abuse, and sexual abuse was tested for predictive impact, with deliberate injury as the dependent variable. Each variable except age was removed from the model while the others were left in to obtain a likelihood ratio chi-square. When age was controlled, sexual abuse was a significant predictor of injury ($\chi^2$=12.12, df=1, p=0.0005), whereas physical abuse ($\chi^2$=1.71, df=1, n.s.) and diagnosis ($\chi^2$=2.68, df=2, n.s.) were not. Fifty-seven percent (N=33) of the subjects received the Earliest Memories Test before the Familial Experiences Interview; the order of administration of the instruments did not predict the frequency of injury responses on the Earliest Memories Test ($\chi^2$=0.07, df=1, n.s.).

The effectiveness of helpers was not associated with reported sexual abuse when all four types of memories were combined. Earliest and next earliest memories and earliest memory of father showed no significant between-group differences. For earliest memory of mother, however, the mean score on effectiveness of helper for the nonabused subjects was significantly higher (i.e., the person was seen as more helpful) than for the abused subjects when borderline and depressed subjects were combined (t=2.33, df=9, p=0.04). When the responses of borderline patients alone were examined, the mean scores were in the expected direction (for the nonabused patients, 4.0; for the abused patients, 1.6±1.3), but the number of scorable memories was small, and no statistical significance was found (t=1.63, df=4, n.s.).

Mean scores on affect tone were in the predicted order: abused subjects in all groups received lower mean scores (i.e., affect tone was more malevolent) than did nonabused subjects (table 3). However, a statistically significant difference was attained only when all subjects were combined and compared. A multiple regression was performed to test sexual abuse and diagnosis simultaneously, while controlling for physical abuse and demographic differences (age: t=2.01, df=56, p=0.05; socioeconomic status: t=2.36, df=49, p=0.02). Affect tone was the dependent variable. Physical abuse was not a significant predictor (t=−1.40, df=47, n.s.), but sexual abuse remained a significant predictor of affect tone (t=−2.46, df=47, p=0.02). Diagnosis showed a trend toward predictive impact (F=3.00, df=2, 46, p=0.06). When diagnosis and sexual abuse were tested simultaneously, neither provided significant additional predictive information over the other.

Scores of extreme malevolence (affect tone scale level 1) were analyzed categorically. Eight subjects (all of them borderline patients reporting sexual abuse) received extreme malevolence scores, yielding a significant difference between the abused and nonabused borderline patients (p=0.05, Fisher's exact test) and between the abused and nonabused subjects when borderline and depressed patients were combined (p=0.007, Fisher's exact test).

We again performed a logistic regression, controlling for socioeconomic status ($\chi^2$=5.18, df=1, p=0.02) but not for age ($\chi^2$=0.42, df=1, n.s.). We tested diagnosis, physical abuse, and sexual abuse as predictors of malevolence. Sexual abuse was a significant predictor ($\chi^2=5.19$, df=1, $p<0.03$), whereas diagnosis ($\chi^2=4.07$, df=2, n.s.) and physical abuse ($\chi^2=2.33$, df=1, n.s.) were not.

## DISCUSSION

Using early memories as projective data for assessing object relations assumes that when subjects reconstruct memories from their multiple stored experiences, the incidents they retrieve reflect chronically activated ways of experiencing and representing the self, others, and relationships that inform daily interpersonal functioning (20, 22). The chosen memories are believed to reflect cognitive and affective organization of past and present interpersonal experiences. This organization then influences processing of information about people now, since current experiences are interpreted in part on the basis of schemas shaped by past experiences.

Given this assumption and certain methodological limitations of our study, our results illustrate the possibility of linking childhood trauma not just to the borderline diagnosis but also to aspects of borderline object relations. Previous studies (26–29) suggest that borderline subjects can be distinguished from various comparison groups on the basis of the malevolent affect tone of relationships depicted in projective tests and self-report data. The present study's finding of an association between reported childhood sexual abuse and projective portrayal of injuries and malevolence supports the findings of those studies and also suggests that some portion of borderline subjects' malevolent object world may be linked more specifically to sexual abuse than to the borderline diagnosis. Further study of borderline subjects' interpersonal difficulties with respect to trauma history may then be fruitful, and if so, future psychodynamic understanding of borderline object relations may need to take specific trauma histories into account. It is important to note that abuse probably occurs in the context of chaotic families that include impaired parents, who either abuse or are unwilling or unable to protect their children. Such parents are also unlikely to have been empathic caretakers during the preoedipal period of their children's lives. However, taken together with other studies, this study offers further evidence that sexual abuse is linked to adult borderline personality disorder in specific ways.

The presence of less effective helpers in only the earliest memory of mother of the subjects who reported sexual abuse must be viewed with caution because there were so few scorable memories. Nevertheless, this response to the "mother" prompt supports some literature on sexual abuse and incest, where the mother is a key figure in helping or failing to help the victim (38).

Three limitations of this study should be noted. First, the data on abuse were retrospective. While informants were not interviewed for all subjects, informants for 11 of the 21 abused borderline subjects were interviewed. In seven (64%) of these cases, the history of sexual abuse was confirmed, primarily by a mother or sibling. Although we cannot be sure that the other reported histories of sexual abuse are true, we believe most of the reports are valid. Herman and Schatzow (39) found that 74% of 53 women reporting sexual abuse were able to corroborate the abuse independently; an additional 9% were found to have strongly suggestive evidence of probable abuse in family members' statements.

A second issue is that the data from the Earliest Memories Test may not be stable over time. Some studies suggest that earliest memories reflect stable aspects of personality (24, 25); others indicate that depression influences the material presented in earliest memories (40, 41). However, depression alone would not account for more memories of injury in a group of patients with borderline personality disorder (the predominant sexually abused group) than in a group of depressed patients.

Another potential problem is that dependent and independent variables may be confounded, particularly with respect to the injury items in the Earliest Memories Test. We attempted to reduce this confounding by eliminating accounts of sexual abuse from the scores for injury; we used logistic regression analyses to protect against the artifact of a double report of physical abuse on the Familial Experiences Interview and the Earliest Memories Test.

The results of this study suggest that clinicians should be aware of malevolent attributions and expectations of injury among sexually abused patients, and particularly among sexually abused borderline patients. Such patients may expect abuse while also wishing for a benevolent "protector." This wish may partially account for borderline subjects' tendency to idealize people while simultaneously expecting these people ultimately to fail them. Further, their malevolent attributions and expectations may be allied with masochistic and self-defeating motivational patterns that have been shaped by the history of abuse and indifference (42). Thus, the patient may expect abuse, set herself up for it, and then find her worst fears confirmed, either through repetition of the actual abuse or through construing as malevolent or injurious interactions that are not.

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# The Face Validity of the *DSM-III* and *DSM-III-R* Criteria Sets for Borderline Personality Disorder

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Objective: *The main objective of this study was to determine the congruence between* DSM-III *and* DSM-III-R *diagnoses of borderline personality disorder derived through the use of semistructured research interviews or given by experienced clinicians after lengthy consultations with an interdisciplinary team.* Method: *The presence of the* DSM-III *and* DSM-III-R *criteria sets for borderline personality disorder was assessed in a study group of 253 patients with personality disorders (148 inpatients and 105 outpatients) by raters who were blind to clinical diagnoses and who used information from two semistructured interviews of proven reliability. These diagnoses were then compared with "longitudinal expert all data" (LEAD) standard clinical diagnoses provided by therapists specifically asked to base their diagnoses on* DSM *criteria.* Results: *Both criteria sets were found to be overinclusive when compared with the LEAD standard. Most criteria were also found to lack specificity. However, the three DSM-III-R criteria that are new or revisions of* DSM-III *criteria were found to be more specific, and raising the cutoff on the* DSM-III-R *criteria from five to six improved specificity.* Conclusions: *Both the* DSM-III *and* DSM-III-R *criteria sets for borderline personality disorder as assessed by semistructured interview lack face validity because they are nonspecific when compared with a rigorous but representative clinical standard, and the results of studies using these criteria sets may prove misleading to researchers and clinicians because they seem to define a nonspecific type of serious character pathology.*

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Since its introduction in 1980, the *DSM-III* criteria set for borderline personality disorder has become the standard for defining the disorder in most clinical settings. It has also been widely used in research studies. A recent MEDLINE computer search indicated that more than 70 studies have used this criteria set to define their borderline subjects. In addition, the reliability of this criteria set has been tested extensively and been found to be adequate (1–3), and, in general, the studies of the diagnostic efficiency of this criteria set (4–8) have found that various combinations of two or three criteria are as efficient in diagnosing borderline personality disorder as the standard scoring algorithm of five out of eight criteria. The *DSM-III* criteria have been shown to define a syndrome whose validity has been supported by the results of studies concerning the phenomenology, familial transmission, treatment response, and longitudinal course of the disorder (9).

The face validity of the *DSM-III* and *DSM-III-R* criteria sets for borderline personality disorder has been tested in only two studies, however. In the first, Spitzer et al. (10) invited psychiatrists to apply draft *DSM-III* criteria for borderline personality disorder to their patients with a clinical diagnosis of borderline personality organization (N=234) and to their patients with a nonpsychotic diagnosis (N=808). At a cutoff of five, this criteria set achieved a sensitivity of 0.77 and a specificity of 0.82. In the second of these studies, Skodol et al. (unpublished 1988 paper) assessed the presence of *DSM-III-R* borderline personality disorder in a group of 30 inpatients with personality disorders using two research interviews—the Structured Clinical Interview for DSM-III-R Axis II Disorders (SCID-II) (11) and the Personality Disorder Examination (2). These findings were then compared with "longitudinal expert all data" (LEAD) standard clinical diagnoses (12), which indicated that 24 (80%) of these patients met the *DSM-III-R* criteria for borderline personality disorder. Both instruments achieved a sensitivity of 0.71, the SCID-II achieved a specificity of 0.50, and the

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Personality Disorder Examination achieved a specificity of 0.33.

The study described in this paper assessed the conditional probabilities of both the *DSM-III* and *DSM-III-R* criteria sets for borderline personality disorder in a study group of 253 patients with a primary axis II clinical diagnosis. It incorporates the methodological advances of the study of Skodol et al. (i.e., independence of clinical and research diagnoses and use of semistructured interviews to assess the presence of diagnostic criteria) and uses a much larger study group of inpatients with personality disorders and outpatients from a broad spectrum of socioeconomic backgrounds.

## METHOD

This study was part of a larger study of the phenomenology of borderline personality disorder. The methodology of this study has been described elsewhere (13). Briefly, 253 patients participated: 148 inpatients at McLean Hospital in Belmont, Mass., and 105 outpatients in treatment at one of three community clinics affiliated with Massachusetts General Hospital. Each patient was initially screened to determine that he or she 1) was between the ages of 18 and 40 years, 2) had normal or better intelligence, 3) had no history or current symptoms of a serious organic condition or major psychotic disorder (i.e., schizophrenia or bipolar disorder), 4) had not abused substances for at least 10 days, and 5) had been given a definite or probable axis II diagnosis by the admitting physician or referring clinician. One of us (M.C.Z.), blind to the patient's clinical diagnosis, obtained written informed consent from each subject and evaluated his or her axis II status by administering the following two research instruments: 1) the Diagnostic Interview for Personality Disorders—a semistructured interview that reliably assesses the presence of the 11 axis II disorders described in *DSM-III* (3), and 2) the Revised Diagnostic Interview for Borderlines (DIB-R)—a semistructured interview that can reliably distinguish patients with clinically diagnosed borderline personality disorder from patients with other axis II disorders (14).

Therapists provided the primary axis II diagnosis for each patient using a form that specifically asked the clinician to use *DSM* criteria in making his or her diagnosis. In addition, these diagnoses were usually made after the patient had been in treatment for at least 2 months, allowing the therapist time to carefully assess the patient's history, review all test results, and consult with an interdisciplinary team, which consisted of a psychiatrist, psychologist, social worker, nurse clinician, and occupational therapist. The presence of the *DSM-III* criteria for borderline personality disorder was assessed by using the appropriate section of the Diagnostic Interview for Personality Disorders. The presence of the three *DSM-III-R* criteria for borderline personality disorder that are new or revisions of *DSM-III* criteria was assessed by one of us (J.H.G.), who was blind to all information concerning each patient, using abstracted information from the DIB-R.

**TABLE 1. Demographic Characteristics of Patients With Clinical Diagnoses of Borderline Personality Disorder and Other Personality Disorders**

| Characteristic | Patients With Borderline Personality Disorder (N=97) | Patients With Other Personality Disorders (N=156) |
|---|---|---|
| Mean | | |
| Number | 16 | 88 |
| Percent | 16.5 | 56.4 |
| Women[a] | | |
| Number | 81 | 68 |
| Percent | 83.5 | 43.6 |
| White | | |
| Number | 97 | 153 |
| Percent | 100.0 | 98.1 |
| Ever married | | |
| Number | 42 | 61 |
| Percent | 43.3 | 39.1 |
| Age (years) | | |
| Mean | 28.4 | 27.6 |
| SD | 6.8 | 6.1 |
| Socioeconomic status[b] | | |
| Mean | 3.5 | 3.4 |
| SD | 1.4 | 1.2 |

[a] The group with borderline personality disorder had significantly more women ($\chi^2=37.7$, df=1, $p<0.0001$).

[b] 1=highest; 5=lowest.

## RESULTS

Ninety-seven (38.3%) of the 253 patients received a primary clinical diagnosis of borderline personality disorder. The remaining 156 patients (61.7%) received the following primary clinical diagnoses: antisocial personality disorder, 45 patients (17.8% of the 253 patients); avoidant personality disorder, 13 (5.1%); compulsive personality disorder, eight (3.2%); dependent personality disorder, 22 (8.7%); histrionic personality disorder, seven (2.8%); narcissistic personality disorder, 14 (5.5%); paranoid personality disorder, one (0.4%); passive-aggressive personality disorder, two (0.8%); schizoid personality disorder, three (1.2%); schizotypal personality disorder, one (0.4%); and mixed personality disorder, 40 (15.8%).

As table 1 shows, the groups of subjects with clinically diagnosed borderline personality disorder and other personality disorders were very similar to each other in terms of age, race, marital status, and socioeconomic status. However, a significantly higher percentage of the patients with borderline personality disorder than those with other personality disorders was female.

Table 2 shows the conditional probabilities of the *DSM-III* and *DSM-III-R* criteria sets for borderline personality disorder. At the standard cutoff of five criteria, the sensitivity and negative predictive power of

**TABLE 2. Conditional Probabilities of *DSM-III* and *DSM-III-R* Criteria Sets and Individual Criteria for Borderline Personality Disorder for 253 Patients With Personality Disorders**

| Criterion | Sensitivity | Specificity | Positive Predictive Power | Negative Predictive Power |
|---|---|---|---|---|
| *DSM-III* criteria set | | | | |
| Cutoff of five | 0.90 | 0.41 | 0.49 | 0.87 |
| Cutoff of six | 0.81 | 0.60 | 0.56 | 0.84 |
| Cutoff of seven | 0.66 | 0.75 | 0.62 | 0.78 |
| *DSM-III-R* criteria set | | | | |
| Cutoff of five | 0.86 | 0.58 | 0.56 | 0.87 |
| Cutoff of six | 0.67 | 0.76 | 0.64 | 0.79 |
| Cutoff of seven | 0.49 | 0.87 | 0.71 | 0.74 |
| Individual criteria | | | | |
| Intense, inappropriate anger[a,b] | 0.90 | 0.28 | 0.44 | 0.81 |
| Affective instability[a,b] | 0.85 | 0.32 | 0.44 | 0.77 |
| Chronic boredom/emptiness[a,b] | 0.94 | 0.21 | 0.43 | 0.85 |
| Intense, unstable relationships[a] | 0.90 | 0.39 | 0.48 | 0.86 |
| Intolerance of aloneness[a] | 0.66 | 0.47 | 0.44 | 0.69 |
| Physically self-damaging acts[a] | 0.66 | 0.63 | 0.52 | 0.75 |
| Other impulsivity[a,b] | 0.91 | 0.26 | 0.43 | 0.82 |
| Identity disturbance[a,b] | 0.79 | 0.44 | 0.47 | 0.78 |
| Intense, unstable relationships[b] | 0.54 | 0.70 | 0.53 | 0.71 |
| Abandonment fear[b] | 0.60 | 0.71 | 0.56 | 0.74 |
| Physicially self-damaging acts[b] | 0.59 | 0.83 | 0.69 | 0.76 |

[a] *DSM-III* criterion.
[b] *DSM-III-R* criterion.

the *DSM-III* criteria set were very high but both specificity and positive predictive power were very low: more than half of our patients given a nonborderline clinical diagnosis met the *DSM-III* criteria for borderline personality disorder as assessed by our research interviews. The conditional probabilities of the *DSM-III-R* criteria set were modestly better at this cutoff: 17% fewer of the patients given a nonborderline clinical diagnosis met the *DSM-III-R* criteria for borderline personality disorder than met the *DSM-III* criteria for borderline personality disorder. As expected, the sensitivity and negative predictive power of both criteria sets decreased and their specificity and positive predictive power increased as the cutoff point was raised. Overall, the cutoff of seven had the best conditional probabilities for the *DSM-III* criteria set, and the cutoff of six was best for the *DSM-III-R* criteria set. However, in both cases, a quarter of our patients given a nonborderline clinical diagnosis were still rated as meeting borderline criteria and a third of our patients with a clinical diagnosis of borderline personality disorder were rated as no longer meeting criteria for the borderline personality disorder.

Table 2 also shows the conditional probabilities of the individual *DSM-III* and *DSM-III-R* criteria for borderline personality disorder. As can be seen, five of the *DSM-III* criteria had high sensitivity and negative predictive power and low specificity and positive predictive power—all three of the affective criteria, one of the interpersonal criteria (intense, unstable relationships), and one of the criteria assessing impulsivity (other impulsivity). The other three criteria—intolerance of aloneness, physically self-damaging acts, and identity disturbance—were less sensitive but more specific. However, their positive and negative predictive power were about the same as those of the other five, less specific *DSM-III* criteria.

All three of the new or revised *DSM-III-R* criteria—frantic efforts to avoid abandonment, which replaced intolerance of aloneness, and more restrictive versions of intense, unstable relationships and physically self-damaging acts—were less sensitive but more specific than the *DSM-III* criteria for borderline personality disorder. In addition, their positive predictive power tended to be somewhat higher and their negative predictive power tended to be somewhat lower.

Table 3 shows the number of patients with various types of nonborderline clinical diagnoses who met the *DSM-III* and *DSM-III-R* criteria for borderline personality disorder as assessed by our diagnostic interviews. All told, 92 (59%) of the 156 patients met the *DSM-III* criteria for borderline personality disorder as assessed by these interviews, including more than half of the patients who received a clinical diagnosis in the dramatic, anxious, or odd cluster. In addition, almost 75% of the patients given a clinical diagnosis of antisocial personality disorder and about half of those given a clinical diagnosis of mixed personality disorder met the *DSM-III* criteria for borderline personality disorder. In two-thirds of the diagnostic categories studied, fewer patients met the *DSM-III-R* criteria than met the *DSM-III* criteria for borderline personality disorder. However, only four of these comparisons met the Bonferroni corrected probability level of $p<0.002$: any type of nonborderline clinical diagnosis ($\chi^2=55.3$, df=1, $p=0.0001$), a nonborderline dramatic cluster clinical diagnosis ($\chi^2=15.0$, df=1, $p=0.0001$), an antisocial clinical diagnosis ($\chi^2=9.8$, df=1, $p=0.002$), and an anxious cluster clinical diagnosis ($\chi^2=25.7$, df=1, $p=0.0001$).

**TABLE 3. Patients With Clinical Diagnoses of Nonborderline Personality Disorders Who Met *DSM-III* and *DSM-III-R* Criteria for Borderline Personality as Assessed by Semistructured Interview**

| Personality Disorder | Times Diagnosed | *DSM-III* |  | *DSM-III-R* |  |
|---|---|---|---|---|---|
|  |  | N | % | N | % |
| Dramatic cluster | 66 | 45 | 68 | 34 | 52 |
| Antisocial | 45 | 33 | 73 | 23 | 51 |
| Histrionic | 7 | 4 | 57 | 4 | 57 |
| Narcissistic | 14 | 8 | 57 | 7 | 50 |
| Anxious cluster | 45 | 25 | 56 | 20 | 44 |
| Avoidant | 13 | 7 | 54 | 7 | 54 |
| Compulsive | 8 | 5 | 63 | 3 | 38 |
| Dependent | 22 | 13 | 59 | 10 | 45 |
| Passive-aggressive | 2 | 0 | — | 0 | — |
| Odd cluster | 5 | 3 | 60 | 2 | 40 |
| Paranoid | 1 | 1 | 100 | 1 | 100 |
| Schizoid | 3 | 1 | 33 | 0 | — |
| Schizotypal | 1 | 1 | 100 | 1 | 100 |
| Mixed | 40 | 19 | 48 | 10 | 25 |
| Any of above | 156 | 92 | 59 | 66 | 42 |

## DISCUSSION

We found that the *DSM-III* criteria set had excellent sensitivity and negative predictive power but poor specificity and positive predictive power in diagnosing borderline personality disorder. The *DSM-III-R* criteria set had modestly better specificity and positive predictive power without substantially lowering sensitivity and negative predictive power. In both cases, raising the cutoff substantially increased specificity and positive predictive power but substantially decreased sensitivity and negative predictive power.

One might argue that this lack of correspondence with clinical diagnoses is unimportant because clinical diagnoses themselves are highly unreliable and of unproven validity. However, they have traditionally been the standard against which official diagnostic criteria sets are compared. Certainly, this was the intent when the *DSM-III* criteria were written. One might also argue that our results are due to psychometric limitations of the Diagnostic Interview for Personality Disorders. However, both the interrater and test-retest reliability of this instrument have been tested extensively and found to be adequate (3). In addition, our *DSM-III-R* specificity results (0.58) are somewhat better than those obtained by Skodol et al. (unpublished 1988 paper), who used two other well-regarded semistructured interviews in a study group of axis II inpatients—the SCID-II (0.50) and the Personality Disorder Examination (0.33). However, Spitzer et al. (10) found a much higher degree of specificity for the *DSM-III* criteria set for borderline personality disorder (0.82) than we did (0.41). This discrepancy is not surprising for two reasons. First, Spitzer et al. were comparing borderline patients to a general group of nonpsychotic patients, but we were comparing borderline patients with those with other forms of serious character pathology. Second, our clinical and research diagnoses were independently determined, but the clinicians in the study of Spitzer et al. not only provided the clinical diagnoses but also rated the presence of the draft criteria for borderline personality disorder.

One might also argue that the differences that we found in our study between clinical diagnoses and those obtained by using information from semistructured interviews were due to the different methodologies employed. However, we obtained better conditional probabilities between clinical diagnoses and DIB-R diagnoses of borderline personality disorder in the same series of patients (14) (sensitivity=0.82, specificity=0.80, positive predictive power=0.74, negative predictive power=0.87), a finding which suggests that the criteria set used to define a study group has importance in itself.

The specificity rates that we found for most of the *DSM-III* criteria for borderline personality disorder were also somewhat lower than those found in previous studies that have assessed the diagnostic efficiency of these eight criteria (4–8). This discrepancy seems to be due to differences in study design. Although our study compared research assessments of the *DSM-III* and *DSM-III-R* criteria for borderline personality disorder with a rigorous but representative clinical standard, most of the diagnostic efficiency studies (4–6) used their research-based diagnoses of *DSM-III* borderline personality disorder as the standard against which the psychometric properties of the specific criteria were measured. This design is circular in nature and assumes a priori the overall validity of the borderline personality disorder diagnosis as defined by *DSM-III.*

Taken together, the results of this study suggest that the diagnostic process used by experienced clinicians is not captured well by our current polythetic algorithms for borderline personality disorder. Our experience suggests that clinicians do not derive a *DSM* borderline diagnosis simply by adding up criteria. Rather, they synthesize the information they have about the patient, taking into account such factors as the severity, chronicity, and clustering of symptoms exhibited by a particular patient in a particular social context. As a result, the clinicians in our study did not give the borderline diagnosis to every affectively labile, impulsive, interpersonally difficult patient in their care. However, both the *DSM-III* and *DSM-III-R* criteria sets for borderline personality disorder as assessed by semistructured interviews seem to encompass a "nonspecific" type of severe character pathology akin to Kernberg's concept of borderline personality organization (15). This problem is highlighted when the criteria sets are used in a study group composed exclusively of seriously disturbed axis II patients. The *DSM-IV* Axis II Work Group of APA is currently considering a number of changes to the *DSM-III-R* criteria set for borderline personality disorder. The results of our study suggest that raising the cutoff from five to six criteria would substantially improve the specificity of the *DSM-III-R* criteria set for borderline personality disorder. Our results also suggest that three criteria are more specific than others, and one might argue that these criteria should receive more weight than the other five, less specific criteria. Given the lack of specificity of the *DSM-III-R* criteria set shown here, some type of change seems necessary, or the results of studies using these criteria to define their borderline study groups may prove misleading to other researchers and clinicians alike.

## CONCLUSIONS

Both the *DSM-III* and *DSM-III-R* criteria sets for borderline personality disorder as assessed by research interviews were found to be overinclusive when compared with a rigorous but representative clinical standard in a study group of patients with personality disorders. Establishing the face validity of these criteria sets should probably have been the first step in defining borderline personality disorder as a psychiatric disorder. However, the influence of *DSM-III* and *DSM-III-R* is so pervasive that this vital step in the validation process seems to have been bypassed as studies involving external validators have already been conducted. An essential next step, then, is to determine whether a criteria set with greater face validity can sustain or, one hopes, strengthen the relationship with such validators. The results of this study both support the need for future criteria sets for borderline personality disorder to reflect informed clinical usage and suggest ways that such face validity can be enhanced.

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# Results of a Survey of Forensic Psychiatrists on the Validity of the Sadistic Personality Disorder Diagnosis

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*Objective: The purpose of this study was to determine how often forensic psychiatrists evaluated individuals with sadistic personality disorder; their views about the usefulness of the diagnosis; the frequency of certain childhood factors; and the sensitivity and specificity of the individual diagnostic criteria. Method: A questionnaire to be answered anonymously was sent to all of the 1,390 members of the American Academy of Psychiatry and the Law. Two hundred seventy-nine usable questionnaires were returned for data analysis. Results: Approximately 50% of the respondents had, at some time, evaluated in a forensic setting a subject who exhibited behavior that met the criteria for the disorder. Four percent of the cases seen in the preceding year by those respondents who had ever seen a case would have met the criteria for the disorder. Most of the forensic psychiatrists who had experience with the disorder believed that the diagnosis is useful for a variety of clinical and forensic purposes, but most also believed that the category has significant potential for being misused in legal settings. Almost all cases described by the respondents involved male patients, and there was frequently a history of childhood abuse and parental loss. The diagnostic criteria in these cases had high sensitivity and specificity. Conclusions: In forensic settings the diagnosis of sadistic personality disorder is probably not rare. The results of this study suggest that the diagnosis has both descriptive and construct validity and that further study of the disorder with the* DSM-III-R *diagnostic criteria is needed.*

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During the development of *DSM-III-R,* psychiatrists who evaluated patients in forensic settings suggested the need for a diagnosis of sadistic personality disorder to describe individuals who demonstrated a long-standing maladaptive pattern of cruel, demeaning, and aggressive behavior toward others but whose personality disturbance was not adequately described by any of the existing *DSM-III* personality disorders. A category called sadistic personality disorder, with a draft text and eight diagnostic criteria, was subsequently developed.

Despite objections to the inclusion of the disorder in *DSM-III-R,* it was eventually included in an appendix to the manual called Proposed Diagnostic Categories Needing Further Study. Since the publication of *DSM-III-R* in 1987, however, there has been little systematic study of the *DSM-III-R* concept of the disorder. Gay and Feister (1), over a period of 7½ years, intensively studied 235 consecutive adults accused of child abuse. Most of the clinical interviews lasted about 10 hours. They found that 5% (N=12) of these subjects met the *DSM-III-R* criteria for sadistic personality disorder. Two-thirds of the cases involved men. For the cases classified as "severe child abuse," 10% met the criteria for the disorder. Of the 12 adults with sadistic personality disorder, only two received another *DSM-III-R* personality disorder diagnosis (narcissistic and antisocial). Nine subjects reported histories of childhood physical abuse, often associated with sexual or emotional abuse or neglect. A surprising finding, consistent with psychoanalytic notions of the importance of object loss in the development of the disorder (2–6), was the large number of cases (N=8) in which there was a history of early loss of a parent or sibling by death or separation.

There were four main purposes of the current study. The first was to survey a large number of forensic psy-

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chiatrists to gather data about how often, in a forensic setting, they evaluated individuals with sadistic personality disorder. The second was to collect information on the views of forensic psychiatrists who had had some experience with the diagnosis about its potential usefulness in a variety of circumstances. The third purpose was to obtain data on a large number of persons with sadistic personality disorder, which could then be used to examine diagnostic overlap and the frequency of histories of various forms of abuse and childhood parental loss or absence. The fourth purpose was to determine the sensitivity of the *DSM-III-R* diagnostic criteria (the frequency of the individual criteria in cases of the disorder). The specificity of the criteria (the frequency of the absence of the criteria in noncases) could be determined by examining a suitable comparison group of patients who did not have the disorder or had a related disorder, such as antisocial personality disorder.

## METHOD

In July 1989 a questionnaire to be answered anonymously was sent to all of the 1,390 members of the American Academy of Psychiatry and the Law, the primary professional organization for psychiatrists who have an interest in or engage in the legal aspects of psychiatric practice. The questionnaire was accompanied by a cover letter signed by the president of the organization. The letter explained the need for obtaining information about the potential value of the diagnosis of sadistic personality disorder in forensic settings. Respondents were urged to return the questionnaire to the first author of this article "even if you believe that the diagnosis of sadistic personality disorder is of no value (or even harmful). It is important that the results of this survey, insofar as possible, represent the membership of the American Academy of Psychiatry and the Law; this will not occur if those who are indifferent or oppose this category do not participate."

## RESULTS

Two hundred seventy-nine usable questionnaires were returned for data analysis. The return rate (20%) is roughly comparable to that obtained in a similar study of the *DSM-III* criteria for borderline and schizotypal personality disorders (7) and to those obtained in other surveys of psychiatrists (8, 9).

The mean±SD age of the respondents was 51±12 years (median=50 years). Eighty-nine percent (N=241) of them were male. (Throughout this article, the percentages reported are based on the number among the 279 respondents who answered each question—excluding instances of missing data and responses of "uncertain"—which varied considerably from question to question.) The mean number of years of professional experience after residency was 19 (median=18). Forty-nine percent (N=136) of the respondents noted their primary professional activity as clinical, 40% (N=109) as forensic, and the small remainder as administrative (6%, N=17), teaching (3%, N=9), or research (1%, N=3).

The mean number of patients personally evaluated by the respondents in a forensic setting in the preceding year was 108. The median number was only 50, because some respondents had evaluated extremely large numbers of patients (28% had 100 or more). The respondents who identified their primary professional activity as forensic had evaluated, on average, a larger number of patients (194 versus 47; $t=8.29$, $df=260$, $p<0.001$).

In order to determine how many respondents had evaluated a patient with sadistic personality disorder in a forensic setting, the questionnaire asked the following: "Have you ever personally evaluated, in a forensic setting, an individual who demonstrated a pervasive pattern of cruel, demeaning, and aggressive behavior that meets the criteria for sadistic personality disorder above?" (the criteria from the *DSM-III-R* appendix). Fifty-two percent (N=141) of the respondents answered yes. Compared to all of the other respondents, the respondents who had identified their primary professional activity as forensic included a significantly larger proportion who answered yes (63%, N=67, versus 44%, N=71; $\chi^2=9.16$, $df=1$, $p<0.001$, with Yates' correction).

The respondents who had ever evaluated a patient with sadistic personality disorder were then asked: "Approximately how many individuals whose personality met the criteria for sadistic personality disorder have you personally evaluated in a forensic setting in the last year?" This group of 141 respondents had personally evaluated, on average, six individuals with sadistic personality disorder, which was approximately 4% of all of the evaluations they had done in the preceding year in a forensic setting. Thus, among respondents who had ever evaluated an individual with sadistic personality disorder in a forensic setting, in the preceding year approximately one in 25 evaluations would have resulted in the diagnosis if it had been available. (If respondents who had never seen a case of sadistic personality disorder are included, approximately one in 40 of all of the forensic evaluations done in the preceding year would have resulted in a diagnosis of the disorder.)

Ninety-seven percent (N=763) of the 787 individuals with sadistic personality disorder evaluated in the preceding year were male. Thirty-seven percent (N=254) also had narcissistic personality disorder, and 75% (N=540) also had antisocial personality disorder (the only other personality disorders inquired about). Thus, although comorbidity of sadistic personality disorder with antisocial and narcissistic personality disorders was high (particularly so with antisocial personality disorder), a substantial proportion of the patients with sadistic personality disorder did not meet the criteria for either of these other personality disorders. For individuals whose pattern of behavior met the criteria for both sadistic and antisocial personality disorders, 73% (N=93) of the respondents thought it would be useful to note both diagnoses. Respondents were encouraged to comment on how they thought this would be useful. The most frequent comment was that the diagnosis of sadistic personality disorder indicated specific features that were usually not present in antisocial personality disorder alone.

The 141 respondents who had at some time evaluated individuals with sadistic personality disorder were asked to note potential uses of the diagnosis. Only 18% (N=25) indicated that the diagnosis of sadistic personality disorder was "not useful for any particular purpose." The other respondents felt that the diagnosis was useful for the following purposes: describing the individual's pattern of behavior (74%, N=104), predicting the individual's likely future pattern of behavior (63%, N=89), providing the court with information that would be relevant in sentencing (59%, N=83), making treatment or management decisions (54%, N=76), and evaluating a parent's fitness for custody (54%, N=76). Only 12% (N=17) noted its use as a psychiatric defense in mitigating responsibility for a crime. Thus, a large proportion of the respondents who had at some time evaluated individuals with the diagnosis believed that it has value for several clinical and forensic purposes.

The questionnaire asked all respondents (whether or not they had ever evaluated an individual with sadistic personality disorder) if they were familiar with instances in which the diagnosis of sadistic personality disorder had been misused (e.g., to excuse criminal responsibility). Of the 279 respondents, only 1% (N=3) said yes. This extremely low proportion is perhaps merely a reflection of the fact that since the diagnosis is not an official category, it has hardly ever been used. However, 66% (N=176) of the respondents believed that if sadistic personality disorder became an official *DSM-IV* diagnosis, it would have considerable potential for being misused in either forensic or clinical settings. The most frequent comment written in on the questionnaire was that it would be misused to mitigate criminal responsibility, especially in child or spouse abuse cases. As one eloquent respondent noted, "The medicalization of evil deeds becomes an avenue of excuses." Some respondents expressed concern that the diagnosis would be used to stigmatize the individual and that it might lead to abuse of incarcerated persons by correctional personnel.

Finally, all respondents were asked, on the basis of their experience and understanding of the concept of sadistic personality disorder, how valuable the category is for possible inclusion in *DSM-IV*. Four response categories were provided. Twenty-nine percent (N=81) of the 279 respondents chose "of no or limited value and likely to be abused if included in *DSM-IV*." Sixteen percent (N=44) chose "perhaps useful, but inadequate data to justify its inclusion in *DSM-IV*." Forty-four percent (N=122) chose "useful, but should only be included in *DSM-IV* if there is research or clinical data demonstrating its utility (validity) as a diagnosis that is distinct from other personality disorders, such as antisocial personality disorder." Eleven percent (N=30) chose "very useful and should be included in *DSM-IV*."

Judgments about the potential value of sadistic personality disorder for inclusion in *DSM-IV* were unrelated to the sex of the respondent, to whether or not the respondent had ever evaluated an individual with the diagnosis, to whether or not the respondent's primary professional activity was forensic, to the number of forensic evaluations done in the preceding year, to the number of cases of sadistic personality disorder seen, or to the number of years of professional experience after residency. The only variable that was related to judgments about the value of the diagnosis for possible inclusion in *DSM-IV* was whether or not the respondent filled out a questionnaire about an actual case that he or she had seen. Whereas 43% (N=70) of the 166 respondents who did not describe a case believed that the diagnosis might be useful for inclusion in *DSM-IV*, 73% (N=82) of the 113 respondents who did describe a case believed that the diagnosis might be useful ($\chi^2$=22.94, df=1, p<0.001).

One hundred thirteen (80%) of the 141 respondents who had at any time evaluated a patient with what they believed to be sadistic personality disorder completed the part of the questionnaire that asked about the most recent patient for whom the respondent believed the diagnosis was appropriate. (Respondents were specifically instructed not to include cases in which the sadistic behavior had been directed toward only one person or had been solely for the purpose of sexual arousal, as in sexual sadism.)

The mean±SD age of the patients in these 113 cases was 35±10 years). All but one (99%, N=111 of 112) were male. The distribution of social classes was 5% (N=6) upper, 41% (N=46) middle, and 54% (N=61) lower. Seventy-nine percent (N=89) were white, 14% (N=16) black, 6% (N=7) Hispanic, and 1% (N=1) other. Most of the patients were evaluated in a jail, in a forensic unit of a hospital, or as part of some other court-ordered evaluation, such as a custody evaluation.

A childhood history of emotional abuse (one or both parental figures being repeatedly hostile, demeaning, or neglecting) was noted for 90% (N=87) of these patients, physical abuse (multiple incidents resulting in bruises or permanent injury) for 76% (N=74), multiple losses (death of or abandonment by parental figures) for 52% (N=48), and sexual abuse for 41% (N=30).

Sixty-seven percent (N=72) of these 113 patients also had antisocial personality disorder, and 47% (N=50) also had narcissistic personality disorder (the only other personality disorders inquired about). Twenty percent (N=21) had neither. Twenty-seven percent (N=28) also had major depression or dysthymia, and 61% (N=66) also had psychoactive substance abuse

**TABLE 1. Sensitivity and Specificity of Proposed Diagnostic Criteria for Sadistic Personality Disorder in *DSM-III-R***

| Criterion | Sensitivity (N=113)[a] | Specificity (N=72)[b] |
|---|---|---|
| 1. Has used physical cruelty or violence for the purpose of establishing dominance in a relationship (not merely to achieve some noninterpersonal goal, such as striking someone in order to rob him or her) | 0.89 | 0.99 |
| 2. Humiliates or demeans people in the presence of others | 0.85 | 0.96 |
| 3. Has treated or disciplined someone under his or her control unusually harshly, e.g., a child, student, prisoner, or patient | 0.71 | 0.96 |
| 4. Is amused by, or takes pleasure in, the psychological or physical suffering of others (including animals) | 0.81 | 0.97 |
| 5. Has lied for the purpose of harming or inflicting pain on others (not merely to achieve some other goal) | 0.65 | 0.99 |
| 6. Gets other people to do what he or she wants by frightening them (through intimidation or even terror) | 0.94 | 0.97 |
| 7. Restricts the autonomy of people with whom he or she has a close relationship, e.g., will not let spouse leave the house unaccompanied or permit teen-age daughter to attend social functions | 0.75 | 0.97 |
| 8. Is fascinated by violence, weapons, martial arts, injury, or torture | 0.75 | 0.93 |

[a] Frequency of the item per 100 cases of sadistic personality disorder, based on data from 113 patients.
[b] 100 minus the frequency of the item, divided by 100, in 72 comparison cases.

or dependence (the only other axis I disorders inquired about).

Table 1 presents the sensitivity of each of the sadistic personality disorder criteria for the entire group. The specificity of each item is also shown for a comparison group of 72 inpatients and outpatients without psychotic or organic disorders who had a variety of axis I (100%) and axis II (64%) disorders. They did not have the diagnosis of sadistic personality disorder but were evaluated on the diagnostic criteria for it by using the *DSM-III-R* version of the Structured Interview for DSM-III Personality Disorders (10). Only two of these patients had antisocial personality disorder.

## DISCUSSION

There are several limitations to this study. First, although efforts were made to encourage an unbiased sample of respondents who felt positively as well as negatively toward the diagnostic category, it is certainly possible that either group may have been overly represented in the 20% of the members who returned completed questionnaires. Second, the study was retrospective and relied on respondents' recollections of cases seen in the preceding year. Despite these limitations, the results support the possible usefulness of the diagnosis.

Although we chose a sample that would maximize the number of possible cases of sadistic personality disorder, we nevertheless were surprised by the relatively high prevalence of the disorder: approximately one in 40 of all individuals evaluated in a forensic setting in the preceding year by the entire group of respondents, and one in 25 of all individuals evaluated by respondents who had at some time evaluated individuals with the disorder. Thus, although the disorder is undoubtedly rare in most clinical settings, in a variety of forensic settings it may not be rare. It should be noted that in other branches of medicine, well-recognized disorders are often extremely rare. Similarly, several well-recognized mental disorders, such as factitious disorders and psychogenic fugue, are extremely rare in general psychiatric settings.

There was an overwhelming predominance of male patients diagnosed as having sadistic personality disorder: 97% in the overall group of 787 cases diagnosed in the preceding year and 99% of the individual cases described. This is consistent with the theoretical and clinical literature.

The results indicate that although many patients with sadistic personality disorder also meet the criteria for antisocial or narcissistic personality disorder, a large proportion do not have either of these comorbid diagnoses. It is likely that in the community, as contrasted with this forensic sample, the comorbidity with antisocial personality disorder would be lower.

Of the respondents who had experience with the diagnosis of sadistic personality disorder, the great majority felt that the diagnosis had potential usefulness for one or more purposes. These included clinical purposes, such as describing the individual's pattern of behavior and making treatment and management decisions, as well as forensic purposes, such as predicting future patterns of behavior, providing the court with information relevant to sentencing, and evaluating fitness for custody. However, an almost equally large proportion believed that if the diagnosis were to become an official *DSM-IV* diagnosis, it would have a significant potential for misuse.

Regarding the value of the diagnosis for *DSM-IV*, there was a wide range of views, with more respondents having a clearly negative view than a clearly positive one. Only 11% believed that there was now sufficient evidence of the validity of the category to justify its inclusion in *DSM-IV*. A major concern of the respondents, despite the majority view that the diagnosis has some usefulness for a variety of clinical and forensic purposes, was that, in the legal system, as an official diagnosis it could be used inappropriately to mitigate criminal responsibility. One solution to this problem would be to have specific laws precluding the use of the diagnosis for this purpose, as has been done in several states for the diagnosis of antisocial personality disorder.

The diagnostic criteria had extremely high sensitivity and, when a heterogeneous group of patients with axis I and axis II disorders was used as a comparison group, extremely high specificity. Thus, the criteria have remarkably high validity in describing a personality pattern. However, the specificity of the criteria for a group of subjects with antisocial personality disorder (the most appropriate comparison group) or for a mixed group of forensic cases (another appropriate comparison group) is not known.

The high frequency of histories of emotional, physical, and sexual abuse found in the group of cases described by the clinicians is consistent with results reported by Gay and Feister (1) in a much smaller group. This high frequency contrasts with the prevalence of such abuse in the general population (11–15) and is consistent with several studies showing the intergenerational transmission of violence. For example, Herrenkohl et al. (16) found that 47% of adults abused as children in turn abused their children, and that 56% of adults who abused their children reported having been abused themselves when they were children. A recent study of childhood trauma in patients with borderline personality disorder (17) reported a similarly high rate of physical abuse (71%).

In the present study, 52% of the patients with sadistic personality disorder reported parental death or abandonment in early childhood, a proportion comparable to that reported by Gay and Feister (1) in their small group and much higher than has been reported in the general community (18–20).

## CONCLUSIONS

The possibility that there is a distinctive childhood history (involving abuse and parental loss) in sadistic personality disorder and the suggestion that the disorder describes a distinctive pattern of behavior which does not overlap completely with antisocial personality disorder indicate that the criteria may indeed define a valid disorder that needs further study.

The *DSM-III-R* criteria for sadistic personality disorder are a tool for identifying individuals who exhibit a pervasive pattern of behavior that not only represents a disability for the perpetrator but, by definition, leads to pain and suffering in others. More empirical data are needed to verify whether this pattern of behavior defines a relatively homogeneous disorder with a distinctive set of determinants, natural history, and response to intervention. If so, the diagnostic criteria can play an important role in directing the attention of clinicians, social service agencies, and mental health researchers to a problem requiring intervention and study.

The criteria for antisocial personality disorder have been a necessary prerequisite for empirical studies of possible etiologic factors and treatment for that disorder. The preliminary findings reported here suggest that the *DSM-III-R* criteria for sadistic personality disorder may be able to play a similar role. If there is not continued study of the treatment of this disorder, the generally poor prognosis of individuals with this condition is not likely to improve, and they and the persons they victimize will continue to suffer.

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# Declining Frequency of Neuroleptic Malignant Syndrome in a Hospital Population

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_Objective:_ *The authors investigated trends in the frequency of neuroleptic malignant syndrome at their center over a period of 8 years and assessed possible reasons for these trends.* _Method:_ *They used previously defined operational criteria in conducting a prospective survey of cases of the syndrome among 2,695 neuroleptic-treated patients from Oct. 1, 1986, to Aug. 31, 1990. The frequency of neuroleptic malignant syndrome during this period was then compared with the frequency in a comparable period prior to October 1986. The investigators also assessed changes between the two periods in risk factors associated with the syndrome, including patients' mean age, sex ratio, diagnoses, and severity of illness; neuroleptic dosage, potency, and route of administration; concomitant use of lithium; and degree of agitation.* _Results:_ *Four cases of neuroleptic malignant syndrome were diagnosed during the more recent 47-month survey period, yielding a frequency of 0.15%±0.05%. This represents a significant decline in the frequency of the syndrome from the estimate of 1.10%±0.40% for the earlier survey period. Significantly fewer patients in the recent period had received intramuscular doses of neuroleptics.* _Conclusions:_ *The frequency of neuroleptic malignant syndrome has declined significantly at this center. The decline appears to be attributable to increasing clinical awareness of the features of the syndrome, allowing early intervention and treatment, and to a reduction in risk factors, such as use of intramuscular neuroleptics.*

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Eleven reports, to our knowledge (1), have provided estimates of the frequency of neuroleptic malignant syndrome; these range from 0.02% (2) to 2.40% (3) among patients surveyed. Only three of these studies (4–6) were performed prospectively, but these also yielded widely disparate estimates, ranging from 0.07% (5) to 2.20% (6). In the study yielding the lowest estimate (5), Gelenberg et al. speculated that conservative neuroleptic dosing strategies, along with a thorough clinical educational program at their center, may have led to early recognition and treatment of incipient cases of neuroleptic malignant syndrome, before the full syndrome appeared.

Other factors may also account for the hundredfold difference in published frequency estimates. For example, possible risk factors for neuroleptic malignant syndrome (7) may vary in different patient populations, so there may be no "true" frequency. However, for all populations, strategies for reducing the risk may be available.

We describe a significant decrease in the frequency of neuroleptic malignant syndrome and increased awareness of the syndrome among clinicians after implementation of a consultation service to evaluate suspected cases at our center.

## METHOD

Beginning in October 1986, a hospital-wide system of surveillance for adverse drug reactions was instituted at McLean Hospital. In addition, a series of in-service lectures on the features of neuroleptic malignant syndrome was presented to physicians and nursing personnel. Patients experiencing persistent or severe extrapyramidal side effects and/or fever while receiving neuroleptics were referred for evaluation. All cases were evaluated within 24 hours by one investigator (P.E.K.) using previously defined operational cri-

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**TABLE 1. Characteristics of Four Patients With Neuroleptic Malignant Syndrome**

| Patient | Age (years) | Sex | Primary Diagnosis | Dose of Neuroleptic | Duration of Exposure to Neuroleptic (days) | Daily Dose of Concomitant Medications | Duration of Symptoms (days) |
|---|---|---|---|---|---|---|---|
| 1 | 38 | F | Major depression with psychotic features | Fluphenazine, 10 mg/day | 14 | Benztropine, 2 mg | 10 |
| 2 | 42 | M | Bipolar disorder, manic | Fluphenazine decanoate, 1.5 cc/week; chlorpromazine, 400 mg/day | 21 | Lithium, 1200 mg (plasma level=0.8 meq/liter); amantadine, 300 mg; clonazepam, 4 mg | 30 |
| 3 | 16 | M | Bipolar disorder, manic | Perphenazine, 16 mg/day | 27 | Benztropine, 1 mg | 7 |
| 4 | 15 | M | Bipolar disorder, manic | Chlorpromazine, 150 mg/day; perphenazine, 16 mg/day | 32 | Propranolol, 30 mg; benztropine, 2 mg; fluoxetine, 60 mg | 4 |

teria that had been applied to suspected cases in earlier surveys (4). Patients underwent appropriate physical and laboratory evaluation and an examination based on the neurologic rating scale of Simpson and Angus (8), which was administered by the same investigator. All patients were also examined during the episode by an internist.

We analyzed cases of neuroleptic malignant syndrome occurring in the 47-month period from Oct. 1, 1986, to Aug. 31, 1990, and compared this period to the 31-month period from March 1, 1984 (when we first began to search for cases of neuroleptic malignant syndrome [9]) to Sept. 30, 1986. It should be noted that two different types of survey were performed during the 31-month period from March 1984 through September 1986 (4, 9). The first part of this earlier survey (9) was largely retrospective and consisted of a search for other suspected cases that had occurred in the year preceding our observation of two cases within a 1-month period. This part of the survey yielded seven cases of neuroleptic malignant syndrome among 483 neuroleptic-treated patients, for a frequency of 1.40%± 0.50%. The second part of the earlier survey (4) was prospective and began at the endpoint of the first. It yielded six patients with the syndrome among 679 patients at risk, for a frequency of 0.90%±0.30%. The combined frequency for the entire 31-month period (13 cases among 1,162 neuroleptic-treated patients) was 1.10%±0.40%.

To control for possible changes in risk factors for the syndrome between the two major survey periods, we compared the mean neuroleptic dose administered to 100 consecutive patients treated in 1985 (during the first survey period) to that administered to 100 patients treated in 1989 (during the second). The margin of error of this estimate (95% confidence interval) is ±6%. To allow for comparison of different neuroleptics, we converted all doses to chlorpromazine equivalents (10). We also recorded the number of intramuscular doses of neuroleptics administered, the percentage of patients receiving high-potency neuroleptics, and the number of patients receiving lithium salts among the two groups of 100 patients sampled. To assess changes in the proportion of patients in each group who displayed severe psychomotor agitation, we recorded the number of incidents of seclusion and restraint for the years 1985 and 1989. We also attempted to compare the mean age, sex ratio, diagnostic distribution, and previous number of psychiatric hospitalizations of the patients admitted in 1985 and those admitted in 1989. Finally, from hospital pharmacy records we calculated the number of patients at risk during the second survey period by recording the number of patients prescribed daily standing doses of neuroleptics. Of 6,951 patients admitted to our center during the 47-month period of the second survey, 2,695 (39%) were treated with neuroleptics. The significance of differences was determined by Fisher's exact test, two-tailed.

## RESULTS

Of 14 patients referred for consultation during the 47-month survey period since October 1986, four had been given diagnoses of neuroleptic malignant syndrome. The clinical features of these patients are summarized in table 1. All four patients were treated with bromocriptine; patients 1 and 2 also required treatment in intensive care units and received intravenous dantrolene sodium. The remaining 10 patients did not meet operational criteria for neuroleptic malignant syndrome. Eight displayed severe extrapyramidal signs; four of these also developed autonomic dysfunction, but none displayed fever. Of the remaining two patients, one had modestly elevated creatine kinase levels associated with agitation but had no other features of the syndrome. The second patient, referred because of fever, was given a diagnosis of bronchitis and displayed no signs of extrapyramidal or autonomic dysfunction. The finding of four cases of neuroleptic malignant syndrome among 2,695 patients receiving neuroleptics yields an estimated frequency of 0.15%±0.05%, as compared to 1.10%±0.40% during the previous 31-month interval—a significant difference.

Differences in risk factors between the two survey periods are displayed in table 2. The percentage of patients receiving intramuscular neuroleptics was significantly lower in the second survey period than in the first.

**TABLE 2. Demographic Factors and Potential Risk Factors for Neuroleptic Malignant Syndrome in Two Surveys of Hospital Patients**

| Variable[a] | 31-Month Survey, March 1, 1984, to Sept. 30, 1986 | 47-Month Survey, Oct. 1, 1986, to Aug. 31, 1990 |
|---|---|---|
| Patients' age (years) | | |
| Mean | 26 | 27 |
| SD | 7.4 | 6.9 |
| Sex ratio of patients (M:F) | 1:1 | 1:1.2 |
| Percentage of patients with diagnosis | | |
| Bipolar disorder | 20 | 22 |
| Schizophrenia | 3 | 4 |
| Major depression | 30 | 32 |
| Organic mental disorder | 3 | 3 |
| Percentage of patients with previous admission | 26 | 25 |
| Number of cases of neuroleptic malignant syndrome | 18 | 4 |
| Number of neuroleptic-treated patients | 1,162 | 2,695 |
| Frequency of neuroleptic malignant syndrome (%)[b] | | |
| Mean | 1.10 | 0.15 |
| SD | 0.40 | 0.05 |
| Neuroleptic dose (mg/day, chlorpromazine equivalents) | | |
| Mean | 487 | 505 |
| SD | 247 | 342 |
| Percentage of patients given intramuscular neuroleptics[c] | 8 | 3 |
| Percentage of patients taking lithium also | 54 | 46 |
| Number of incidents of seclusion and restraint | | |
| Mean | 9.5 | 11.5 |
| SD | 4.0 | 6.4 |
| Percentage of patients taking high-potency neuroleptics | 57 | 51 |

[a] The first four variables (age, sex ratio, diagnosis, and previous admissions) refer to the entire hospital population in each survey period. The last five variables (neuroleptic dose, intramuscular neuroleptics, lithium, seclusion and restraint, and high-potency neuroleptics) refer only to the subset of patients in each survey period who received neuroleptics. See text for methods of calculating these values.

[b] Significant difference between groups ($\chi^2=19.5$, df=1, $p<0.001$).

[c] Significant difference between groups ($\chi^2=47.1$, df=1, $p<0.001$).

## DISCUSSION

Several factors might account for the nearly tenfold decrease in the frequency of neuroleptic malignant syndrome between the first (before October 1986) and second (after October 1986) survey periods. First, earlier detection and treatment of neuroleptic-induced side effects may have prevented emergence of the full syndrome. The possible importance of early intervention is supported by the observation that severe extrapyramidal side effects, often accompanied by autonomic disturbances, were present in all but two patients referred for evaluation, but prompt treatment of these patients apparently prevented progression to fever in a majority of cases.

Second, the observed decrease in frequency may have been due to a decline in risk factors. In particular, we found a highly significant decrease in the use of intramuscular neuroleptics between the first and second survey periods. Interestingly, in a previous case-control study from our center (7), use of intramuscular neuroleptics was found to represent the most important risk factor for the development of neuroleptic malignant syndrome.

In conclusion, the results of this study suggest that the frequency of neuroleptic malignant syndrome may be reduced by increasing clinical awareness of its cardinal features, by treating neuroleptic-induced extrapyramidal and autonomic side effects at their earliest emergence, and by minimizing risk factors such as use of intramuscular neuroleptics.

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# Correlates of Risk of Suicide in Violent and Nonviolent Psychiatric Patients

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Objective: *This study was designed to identify variables that correlate with the risk of suicide in two patient groups that differ mainly in their level of expressed aggression.* Method: *Twenty-eight psychiatric patients with a history of violent behavior who were in a forensic psychiatric facility were tested and compared to 28 psychiatric inpatients without a history of violence who were admitted to a large municipal hospital. Measures used included a battery of self-report questionnaires, with acceptable reliability and validity, that provided indices of risk of suicide, risk of violence, impulsivity, anger, anxiety, and various mood states.* Results: *The two groups, matched on demographic variables and overall risk of suicide, differed significantly on the measured risk of violence. The two groups showed similar patterns of correlations between risk of suicide and such variables as risk of violence, anger, fear, state and trait anxiety, lack of impulse control, suspiciousness, and rebelliousness. They differed in the correlation between suicide risk and depression. In the nonviolent patients there was a high correlation between risk of suicide and sadness; in the violent patients there was no correlation between these variables.* Conclusions: *The low correlation between sadness and risk of suicide in the violent patients, and the low prevalence of affective disorder diagnoses in these patients compared to other patients, suggests that suicidal risk should be managed differently in highly violent patients than in others.*

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A number of investigators have reported on the measurement of risk of suicide and its correlates, such as lowering of mood, anxiety, anger, and impulsivity (1, 2). At the same time, other researchers have found significant correlations between risk of violence and similar variables (3–5). The high correlation between violent behavior and suicidal behavior has been well documented epidemiologically (6), clinically (7, 8), and psychometrically (9, 10) and lends support to the notion that both outwardly and inwardly directed aggression may have a common underlying basis. We have also previously reported significant correlations between mood, anxiety, anger, impulsivity, risk of violence, and risk of suicide and have hypothesized that since evidence exists that all these psychopathological dimensions are related to abnormal serotonin function (11), such psychometric correlations may indeed reflect a common biochemical foundation (10).

Although a number of investigators have examined the psychological profile of violent offenders (12), few have focused on risk of suicide in this population (13, 14). The present study was designed to determine the similarities and differences in the correlates of risk of suicide found in psychiatric inpatients without a history of violent behavior and in a group of incarcerated psychiatric patients with a marked history of violent behavior.

## METHOD

### *Subjects*

Two groups of subjects were compared. The first group consisted of 28 male patients hospitalized in a state forensic maximum security hospital. Twenty-three had committed crimes and were hospitalized because of associated severe psychiatric disturbance, while the other five patients were hospitalized for excessively unmanageable violent behavior in regular

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state mental hospitals. These violent patients were compared with 28 male psychiatric inpatients hospitalized at a large general municipal hospital.

The state forensic hospital is a maximum security institution with a current population of 96 men. The average length of stay is 143 days. The general municipal hospital is a large city hospital with a catchment area of 250,000 inhabitants, mainly lower middle class; the catchment area is approximately one-third white, one-third black, and one-third Hispanic. In the psychiatric inpatient service the average stay is about 3 weeks, and rehabilitation and milieu treatment approaches are emphasized.

Forensic patients were selected because of a long history of violence and assaultiveness. They had been convicted of murder (N=15) or other violent crimes or were too violent to be hospitalized in a regular mental health facility. We selected a matched sample from a large group of inpatients without a history of violent behavior in the municipal hospital. The two groups were individually matched for age, past number of suicide attempts (defined as serious, potentially lethal acts against the self with a definite intent to die), and risk of suicide as measured by the Suicide Risk Scale (15). None of the patients in either group was actively psychotic at the time of the investigation. It was not possible to match for diagnosis.

Primary diagnoses were made according to *DSM-III-R* criteria on the basis of chart reviews, a diagnostic interview with the patient, and consultation between the research team and the treatment staff at each institution. The primary diagnosis was that diagnosis which by consensus of the treatment and research teams accounted for the major part of the patient's clinical picture. Thirteen forensic patients were diagnosed as being schizophrenic, 15 as having borderline personality disorder, and none as having a diagnosis of mood disorder. The average age of these patients was 29 years, and the average length of stay was 150 days. All were receiving psychotropic drugs and psychosocial treatment at the time of the study. Six municipal hospital patients were given a diagnosis of schizophrenia; 15, borderline personality disorder; and seven, major depression. The average age of these patients was approximately 30 years, and all were receiving psychotropic drugs and psychosocial treatment.

All patients whose therapists agreed to their participation and who were willing to participate were eligible for the study, with the exception of those under 18 or over 64 years of age, those with significant thought disturbances, those with organic brain syndromes, and those with a lack of fluency in English. All patients signed informed consent forms.

### *Assessment*

An experienced psychiatrist interviewed each patient about the reason for admission. On the basis of this interview, a chart review, and a discussion with the ward psychiatrist, the research team reached a consensual *DSM-III-R* diagnosis.

A battery of self-report test measures was administered during the first week of admission. Each test measures one of the psychometric variables included in the study (i.e., risk of suicide, risk of violence, impulsivity, anxiety, anger, and mood). A psychiatrist was present with each patient at all times and, if requested, would read the questions and record the patient's answers. The following tests were administered.

*Risk of suicide.* This variable was measured with the Suicide Risk Scale. The scale consists of 26 items answered yes or no by the patient. The scale includes items on past history of suicide attempts, present strength of suicidal impulses, feelings of depression and hopelessness, and other items that have been reported to be associated with suicide attempts (15).

The internal reliability of this scale has been found to be 0.84, indicating high correlations among the items. The scale has been given to psychiatric outpatients and inpatients. It correlates with clinicians' judgments of suicide risk in patients. Scores on the Suicide Risk Scale have been shown to discriminate between a group of outpatients clinically evaluated as having suicidal symptoms and a group of patients with no suicidal symptoms. It also has been shown to discriminate between inpatients who have made a suicide attempt in the past and those who have never made such an attempt. Its sensitivity and specificity are reasonable (15).

*Risk of violence.* This measure was assessed with the Past Feelings and Acts of Violence Scale. This scale consists of 12 items answered on a 3-point continuum of frequency. The patient is asked about acts of violence against others, the carrying and use of weapons, arrests, and loss of temper. The internal reliability of the scale is 0.77, indicating high correlations among the items. The scale (in a slightly longer version) has been given to hundreds of individuals representing diverse groups including college students, pain patients, patients with epilepsy, self-referred violent patients, and prisoners. The results show clear discrimination among most of the groups on average level of expressed violence, with the prisoners and self-referred violent patients scoring the highest and the epileptic patients scoring the lowest (16). In a study of psychiatric inpatients (17), the scale significantly discriminated between patients reporting violent acts toward others and patients reporting neither suicidal nor violent acts. It has also been used in the study of neuropsychiatric patients and to identify subgroups of violent individuals (18). The sensitivity and specificity of the scale have also been determined (17).

*Impulsivity.* This variable was measured by the Impulsivity Scale, which consists of 15 items answered on a 3-point frequency scale. These items ask about the tendency to engage in impulsive, spur-of-the-moment behaviors, all of which reflect possible loss of control. The scale has an internal reliability of 0.79, indicating a high correlation among items. It has been further described by Plutchik and van Praag (9).

*State and trait anxiety.* This item was measured by the Spielberger State-Trait Anxiety Scale (19), which has been widely used in psychometric research. The scale consists of two forms, one that relates to the patient's present feelings (state anxiety) and the other relating to chronic, long-term anxiety (trait anxiety).

*Mood.* Mood was measured by the Mood Adjective Checklist (20), which measures eight mood constellations. Each mood constellation consists of a number of related adjectives, each rated on a 0–100 scale by the patient. For example, the happiness mood constellation consisted of the terms "interested," "sociable," "satisfied," and "happy," while the sadness constellation consisted of the words "sad," "worried," "unhappy," and "disappointed"). The final score for each mood is the average of the ratings of each term describing that mood. The other six mood constellations were described by the following terms: "calmness," "fear," "instability," "suspiciousness," "rebelliousness," and "expectancy."

*Anger.* Anger was measured by the Multidimensional Anger Inventory developed by Siegal (21). The scale measures different dimensions of anger, but in this study only the total anger score was used. The scale has been shown to be reliable, and there is some evidence for good validity. It also correlates with other widely used measures of hostility and aggression (21).

### *Data Analysis*

The two groups were compared on each variable by means of t tests. Within each group of patients, Pearson product-moment coefficients were used to correlate the results of all test measures with risk of suicide. The test measures were then correlated with risk of suicide after the risk of violence was partialed out. This technique was used because previous research has shown that risk of violence and risk of suicide are highly correlated (r=0.45) (2). Therefore, it should be possible by the use of partial correlation to identify which variables correlate with risk of suicide without the influence of the risk of violence measure.

## RESULTS

Due to the selection and matching procedures, there was no difference between the violent (forensic hospital) and the nonviolent (general municipal hospital) groups in terms of average age (29 versus 30 years), gender, number of patients with a history of suicide attempts (in each group, 10 patients had no history of suicide attempts, six had made one suicide attempt, and 12 had made two or more suicide attempts), or score on the Suicide Risk Scale (mean±SD scores= 11.5±0.9 for the violent patients and 11.8±0.9 for the nonviolent group).

The violent forensic group had significantly higher scores than the nonviolent group on the Past Feelings and Acts of Violence Scale (t=2.15, df=54, p<0.05). Since these patients were selected on the basis of a history of violence, this finding provides external validation of the violence scale.

**TABLE 1. Psychopathology Scores of 28 Violent Patients From a Forensic Psychiatric Institution and 28 Nonviolent Psychiatric Patients From a Municipal Hospital**

| | Violent Group | | Nonviolent Group | | |
|---|---|---|---|---|---|
| Variable | Mean | SD | Mean | SD | t (df=54) |
| Impulsivity[a] | 18.5 | 7.7 | 17.9 | 6.4 | 0.32 |
| Anger[b] | 58.9 | 23.3 | 68.5 | 22.5 | 1.56 |
| Risk of violence[c] | 10.0 | 5.4 | 7.1 | 4.6 | 2.15[d] |
| Mood[e] | | | | | |
| Calmness | 64.0 | 25.1 | 63.5 | 31.1 | 0.08 |
| Fear | 39.6 | 30.2 | 34.5 | 27.5 | 0.66 |
| Sadness | 45.3 | 32.4 | 52.5 | 28.3 | 0.37 |
| Instability | 35.8 | 33.0 | 38.9 | 27.9 | 0.38 |
| Suspiciousness | 42.0 | 33.7 | 36.3 | 30.7 | 0.65 |
| Rebelliousness | 34.1 | 25.9 | 41.9 | 28.7 | 1.07 |
| Expectancy | 56.9 | 28.5 | 49.4 | 26.0 | 1.04 |
| Happiness | 63.2 | 20.8 | 54.0 | 27.4 | 1.41 |
| Anxiety[f] | | | | | |
| Trait | 43.1 | 14.7 | 43.6 | 11.0 | 0.15 |
| State | 41.7 | 16.9 | 41.7 | 14.9 | 0.00 |

[a] Impulsivity Scale (9).
[b] Multidimensional Anger Inventory (21).
[c] Past Feelings and Acts of Violence Scale (15–18).
[d] p<0.05.
[e] Mood Adjective Checklist (20).
[f] Spielberger State-Trait Anxiety Scale (19).

Table 1 presents the means and standard deviations for all the psychometric variables for both groups. It also shows the comparison by t test between the groups for all the psychometric variables. There were no significant differences between the violent and the nonviolent groups on any of the variables apart from risk of violence.

Since we found that risk of suicide and risk of violence were significantly and positively correlated in both the forensic (r=0.42) and the municipal hospital (r=0.33) groups, partial correlations for each group were calculated and compared. This is shown in table 2.

The analysis of correlations in the violent group showed that lack of impulse control, anger, fear, instability, suspiciousness, rebelliousness, and state and trait anxiety were positively correlated with risk of suicide, whereas calmness was negatively correlated with risk of suicide. In the nonviolent group a similar pattern existed. There were, however, two striking differences in the pattern of correlations between the groups after risk of violence was partialed out.

In the forensic patients, but not the municipal hospital patients, there was a highly significant correlation between anger and risk of suicide (r=0.71, p<0.001). There was a significant correlation between sadness and suicide risk in the nonviolent patients (r=0.52, p<0.01) but not in the violent patients. In addition, happiness correlated negatively and significantly with

**TABLE 2. Correlations of Psychopathological Variables With Risk of Suicide for 28 Violent Patients From a Forensic Psychiatric Institution and 28 Nonviolent Psychiatric Patients From a Municipal Hospital**

| | Correlation (r) of Psychopathology Score With Suicide Risk | | | |
|---|---|---|---|---|
| | Violent Group | | Nonviolent Group | |
| Psychopathological Variable | Overall (df=26) | Risk of Violence Partialed Out (df=26) | Overall (df=26) | Risk of Violence Partialed Out (df=26) |
| Impulsivity | 0.59 | $0.51^a$ | 0.32 | $0.34^b$ |
| Anger | 0.77 | $0.71^c$ | 0.43 | 0.30 |
| Risk of violence | 0.42 | — | 0.33 | — |
| Mood | | | | |
| Calmness | −0.47 | $-0.35^b$ | −0.23 | $-0.32^b$ |
| Fear | 0.61 | $0.53^a$ | 0.39 | $0.39^b$ |
| Sadness | 0.27 | 0.12 | 0.54 | $0.52^a$ |
| Instability | 0.58 | $0.48^a$ | 0.18 | 0.15 |
| Suspiciousness | 0.56 | $0.44^b$ | 0.51 | $0.43^b$ |
| Rebelliousness | 0.61 | $0.52^a$ | 0.37 | 0.28 |
| Expectancy | 0.18 | 0.06 | −0.20 | −0.30 |
| Happiness | −0.22 | −0.02 | −0.46 | $-0.57^a$ |
| Anxiety | | | | |
| Trait | 0.67 | $0.61^c$ | 0.62 | $0.59^c$ |
| State | 0.76 | $0.71^c$ | 0.44 | $0.41^b$ |

[a] $p<0.01$.
[b] $p<0.05$.
[c] $p<0.001$.

suicide risk in the nonviolent patients ($r=-0.57$, $p<0.01$) but not in the violent patients.

## DISCUSSION

The two groups that we studied were different with regard to severity of violent behavior, reason for admission, and *DSM-III-R* primary diagnoses. Despite these differences, we found that there were similar patterns of significant and positive correlations between impulsivity, anger, anxiety, fear, suspiciousness, and rebelliousness and the risk of suicide in both groups. These results are similar to those in our previous studies (2, 10). If this finding can be replicated in other diverse psychiatric patients, it would lend further support to the theory that these psychopathological dimensions may have a common biological substrate (11).

Of interest is the finding that the violent group showed no correlation between sadness and suicide risk, whereas the nonviolent group demonstrated a high correlation between these variables. One possible explanation for this discrepancy is the low prevalence of affective disorder in the violent group. Of the 28 patients from the forensic hospital, none had a diagnosis of mood disorder. Examination of the records of all 96 patients currently at the forensic institute shows that only six patients (6.25%) have been diagnosed as having a mood disorder; the prevalence of affective disorder in the large municipal hospital psychiatric wards is approximately 15% to 20%.

This observation raises the possibility that violent patients in general may have a low rate of affective disorder. A similar observation has been made by Keltigangas (22), who found that the majority of incarcerated violent offenders do not report depressive symptoms. In a study by Apter et al. (8), adolescents with severe conduct disorder who showed little depressive symptoms were found to be more suicidal than adolescents with major affective disorder.

In order to explain the low correlation between sadness and suicide risk in the violent patients, we hypothesize an ego defect in this group of patients that inhibits the expression of depressive symptoms. Alternatively, these patients may tend to act out sad feelings through acts of violence that may be in the form of self-injury or aggression toward others. This hypothesis is supported by our finding of a significant correlation between anger and suicide risk in violent patients but not in nonviolent patients.

Given these findings and postulates, we suggest that the management and therapy of suicidal behavior in the two groups of patients described earlier require substantial differences. The focus in depression-related suicidality would be on antidepressant medications and psychotherapies shown to be useful in depression, such as cognitive therapy. However, the focus in aggression-related suicidality would be on the underlying impulsiveness, medications such as lithium or the recently developed serenic class of drugs (23), and varied behavioral techniques.

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# Psychiatric Inpatient Care in the VA: Before, During, and After DRG-Based Budgeting

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*Objective: The authors examined the impact of budgeting based on diagnosis-related groups (DRGs) on inpatient psychiatric care in Department of Veterans Affairs (VA) medical centers. DRG-based budgeting was implemented by the VA in 1984 and suspended in 1988. Method: Computerized discharge abstracts were obtained for all episodes of VA inpatient care occurring from 1980 through 1989. The number of discharges per year, number of unduplicated patients treated, mean length of stay, total number of bed days of care per unique patient per year, readmission rates, and number of episodes of care per operational bed were determined for psychiatric and nonpsychiatric (medical-surgical) hospitalizations occurring before, during, and after DRG-based budgeting was in effect. Results: In the case of VA psychiatric care, DRG-based budgeting was associated with more episodes of care, shorter lengths of stay, higher readmission rates, and more episodes of care per occupied bed. DRG-based budgeting had similar effects on medical-surgical care, although an increase in the number of episodes of care was not observed. During the first year after this funding mechanism was suspended, changes in both psychiatric and medical-surgical care that were related to DRG-based budgeting were slowed and, in some cases, reversed. Conclusions: Both psychiatric and medical-surgical inpatient care in the VA were sensitive to changes in funding mechanisms. These changes were generally similar to those observed in psychiatric care provided by non-VA hospitals reimbursed under Medicare's DRG-based prospective payment system.*

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The practice of inpatient medicine in the United States has been deeply influenced by the introduction, in 1983, of a prospective payment system (PPS) based on diagnosis-related groups (DRGs) for Medicare reimbursement (1). Thus far, however, private psychiatric hospitals have been exempted from Medicare's DRG-based PPS, and general hospital psychiatric units have been given the option of applying for exemption. In October 1984 the Department of Veterans Affairs (VA) introduced the VA resource allocation methodology, a budgeting system based on DRGs. In contrast to the Medicare model, the VA resource allocation methodology offered no exemptions for inpatient psychiatric care.

In a previous paper (2) we showed that the VA resource allocation methodology had a major impact on inpatient psychiatric care during the first 4 years it was in effect. The number of episodes of care delivered and the number of unduplicated patients treated increased by 28.7% and 15.5%, respectively, and lengths of stay declined by 36.9%. In September 1988, 4 years after its implementation, the VA resource allocation methodology was suspended because of concerns that it was driving the VA health care system to provide a volume of services that exceeded its resource base (3). To our knowledge, this is the first instance in which a PPS was implemented and then withdrawn from use in a national health care system. The suspension of the VA resource allocation methodology provides a unique opportunity to examine the sensitivity of a national health care system to a series of changes in payment mechanisms.

In this paper we assess the impact of these changes on the VA mental health system by examining data on inpatient VA psychiatric care during the 4 years before the resource allocation methodology was introduced, the 4 years after it was introduced, and the first year after it was suspended. To determine whether the observed changes were unique to VA psychiatric care, we also reviewed data on medical-surgical inpatient care

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in the VA and on psychiatric care provided by non-VA hospitals reimbursed by Medicare's DRG-based PPS.

## METHOD

Data on both psychiatric and medical-surgical discharges were derived from the VA's computer-based discharge abstract file, the Patient Treatment File. All VA discharges during fiscal years 1980, 1984, 1988, and 1989 were included. Those in which the primary discharge diagnosis was a psychiatric disorder, including substance abuse disorders (*ICD-9* codes 290.00–319.99), were analyzed separately from those in which the primary discharge diagnosis was a nonpsychiatric (i.e. medical or surgical) disorder. Data derived from the Patient Treatment File include the number of episodes of care (by diagnostic category), the number of unduplicated individuals discharged, the mean length of stay per episode, the total number of bed days of care per patient per year, and the percentage of discharges followed by readmission within 14 days. Data from the annual census of VA inpatients (4) were used to estimate the mean number of occupied beds per year and to identify the number of beds occupied by long-term care patients (those hospitalized for 1 year or more at the time of the census). Data from the Patient Treatment File and from the annual census were combined to compute the number of discharges per occupied bed per year. These analyses were conducted separately for psychiatric and nonpsychiatric discharges.

Comparisons were made between data from fiscal years 1980 and 1984 (the last 4 years before the application of the VA resource allocation methodology), 1984 and 1988 (the 4 years after application of the VA resource allocation methodology), and 1988 and 1989 (the first year after the suspension of application of the VA resource allocation methodology). Percent changes in the years before and during application of the resource allocation methodology are presented as mean annual percent changes to facilitate comparison with data for 1988–1989.

## RESULTS

Consistent trends in VA inpatient psychiatric care during the years before application of the VA resource allocation methodology included declining numbers of episodes of care and of patients treated, increasing lengths of stay per episode of care, and increasing numbers of bed days of care per patient per year (table 1). These trends all reversed direction to a substantial degree under the VA resource allocation methodology. Readmission rates, which were largely unchanged during the years before application of DRG-based budgeting, increased 8.7% per year between 1984 and 1988, probably as a consequence of declining lengths of stay. The mean number of beds occupied by patients with primary psychiatric diagnoses and the number of beds occupied by long-term psychiatric patients declined during the VA resource allocation methodology years at about the same rate as it had during the years before DRG-based budgeting was instituted. The number of episodes of care delivered per occupied bed increased markedly, by 13.1% per year.

During fiscal year 1989, the first year after the suspension of application of the VA resource allocation methodology, trends stimulated by DRG-based budgeting were attenuated and, in several instances, reversed. The number of episodes of care and unique patients treated annually, which had increased under the VA resource allocation methodology, declined (table 1). Lengths of stay and annual bed days of care per patient, which declined during DRG-based budgeting, continued to decline during fiscal year 1989, but at a slower rate (table 1). During the first year after the suspension of application of the VA resource allocation methodology, for the first time in at least 9 years, the percentage of discharges followed by readmission within 14 days decreased, the number of patients hospitalized for 1 year or more at the time of the annual census increased, and the number of episodes of care delivered per occupied bed decreased. The diagnostic case mix appears to have been unaffected by either the VA resource allocation methodology or its suspension (data available on request). Developments in the care of patients with nonpsychiatric primary diagnoses followed generally similar trends (table 1). Among these patients, however, workload measures (the number of episodes of care and the number of unique patients treated) were increasing at a substantial rate during the years before application of the VA resource allocation methodology, and lengths of stay were already declining. Both readmission rates and the number of episodes per occupied bed were increasing, most likely as a result of the declining mean length of stay.

During the DRG-based budgeting years the mean length of stay for medical-surgical episodes of care and the mean number of bed days of care per patient per year declined at a greater rate than previously. In contrast to the findings for VA psychiatric care, virtually no change was noted in the total number of episodes of care or the number of unduplicated medical-surgical patients treated (table 1).

As with psychiatric episodes of care, the first year after the suspension of application of the VA resource allocation methodology saw a decline in gross workload measures for medical-surgical episodes of care, a slower decline in mean length of stay, and a slower increase in the number of episodes of care delivered per bed. The number of long-stay medical-surgical patients continued to decline, but at a reduced rate (table 1).

## DISCUSSION

These VA data clearly demonstrate the sensitivity of inpatient psychiatric care, as well as medical-surgical

**TABLE 1. VA Inpatient Care for Patients With Primary Psychiatric and Nonpsychiatric Diagnoses Before Implementation, During, and After Suspension of Implementation of the Resource Allocation Methodology**

| | Before | | | During | | After | |
|---|---|---|---|---|---|---|---|
| Item | 1980 | 1984 | % Change/ Year 1980–1984 | 1988 | % Change/ Year 1984–1988 | 1989 | % Change/ Year 1988–1989 |
| Number of episodes of care/year | | | | | | | |
| Psychiatric patients | 211,439 | 192,874 | −2.2 | 248,160 | 7.2 | 233,912 | −5.7 |
| Nonpsychiatric patients | 685,116 | 758,900 | 2.7 | 777,337 | 0.6 | 737,653 | −5.1 |
| Number of unique patients/year | | | | | | | |
| Psychiatric patients | 147,546 | 136,106 | −1.9 | 157,194 | 3.9 | 148,952 | −5.2 |
| Nonpsychiatric patients | 470,784 | 497,585 | 1.4 | 478,797 | −0.9 | 455,430 | −4.9 |
| Mean length of stay/episode (days) | | | | | | | |
| Psychiatric patients | 52.4 | 56.7 | 2.1 | 35.8 | −9.2 | 34.1 | −4.7 |
| Nonpsychiatric patients | 21.0 | 17.9 | −3.7 | 13.6 | −6.0 | 13.3 | −2.2 |
| Number of bed days of care per patient/year | | | | | | | |
| Psychiatric patients | 75.1 | 80.4 | 1.8 | 56.5 | −7.4 | 53.5 | −5.3 |
| Nonpsychiatric patients | 30.6 | 27.1 | −2.8 | 22.1 | −4.7 | 21.6 | −2.3 |
| Patients readmitted within 14 days after discharge (%) | | | | | | | |
| Psychiatric patients | 13.8 | 14.0 | 0.4 | 18.9 | 8.7 | 16.0 | −15.3 |
| Nonpsychiatric patients | 9.7 | 11.0 | 3.4 | 13.9 | 6.6 | 13.6 | −2.2 |
| Mean number of beds occupied/day[a] | | | | | | | |
| Psychiatric patients | 29,496 | 25,248 | −3.6 | 21,322 | −3.9 | 19,441 | −8.6 |
| Nonpsychiatric patients | 40,126 | 34,757 | −3.3 | 27,347 | −5.3 | 24,983 | −8.9 |
| Number of long-term patients[b] | | | | | | | |
| Psychiatric patients | 9,098 | 6,609 | −6.8 | 4,374 | −8.5 | 4,434 | 1.4 |
| Nonpsychiatric patients | 2,727 | 2,294 | −4.0 | 1,597 | −7.6 | 1,599 | 0.1 |
| Number of episodes per occupied bed | | | | | | | |
| Psychiatric patients | 7.2 | 7.6 | 1.6 | 11.6 | 13.1 | 12.0 | 3.4 |
| Nonpsychiatric patients | 17.1 | 21.8 | 7.0 | 28.4 | 7.5 | 29.5 | 3.9 |

[a] Data are from VA annual reports for 1979, 1984, 1988, and 1989 (4).
[b] Length of stay more than 1 year; data are from VA annual reports for 1979, 1984, 1988, and 1989 (4).

care, to a series of changes in funding mechanisms. It is notable, for comparison purposes, that 2 years after implementation of Medicare's DRG-based PPS, psychiatric length of stay declined by 10%–20% in scatter beds subject to PPS and by 10% in nonexempt psychiatric units (5). Although lengths of stay in VA hospitals are generally greater than those of non-VA general hospitals, the annual reduction in mean length of stay in VA hospitals under the resource allocation methodology was similar in magnitude to that observed in non-VA hospitals under PPS. Changes in mean length of stay for medical-surgical care in VA hospitals were also similar in magnitude to those observed for psychiatric care. DRG-based budgeting thus appears to have had a similar impact on mean length of stay for VA psychiatric patients, non-VA psychiatric patients, and VA medical-surgical patients.

Differences emerge, however, when we consider the impact of DRG-based budgeting on the volume of inpatient care delivered. Although the VA's resource allocation methodology stimulated a striking increase in both annual episodes of care and the number of unduplicated individuals treated for psychiatric disorders, Medicare's PPS was associated with an overall decline in episodes of inpatient psychiatric care (6). Although data on the delivery of outpatient care are not available for either VA or non-VA health care systems, it is possible that Medicare's PPS was associated with a general shift away from inpatient care and toward outpatient care funded through other mechanisms. In contrast, the VA resource allocation methodology appears to have stimulated an increase in the use of psychiatric hospital treatment, possibly through a lowering of thresholds for admission.

It is notable that the volume of medical-surgical care in VA medical centers was increasing before the VA resource allocation methodology was implemented and slowed considerably under DRG-based budgeting, the reverse of the pattern observed for psychiatric care. During the years of the VA resource allocation methodology, the aging of the veteran population may have been associated with a reduction in acute inpatient psychiatric treatment and an increased demand for medical treatment. DRG-based budgeting incentives for increasing the number of episodes of hospital care had a greater impact on psychiatric care than on medical-surgical care, perhaps because psychiatric services could be expanded without investment in costly equipment or supplies. Reductions in care available from other public sector mental health providers during the 1980s (7) may also have increased demand for VA services.

In our previous paper (2), we showed that although the VA resource allocation methodology purported to offer fiscal incentives for increased efficiency, inflation and a declining psychiatry funding base meant that few additional resources were obtained by psychiatry programs as a result of their increased efficiency (1). Changes in clinical practice associated with both implementation of the VA resource allocation methodology and with its suspension, therefore, cannot be attributed to actual changes in funding. It appears that the influence of the VA resource allocation methodology derived from its theoretical promise of fiscal rewards and its embodiment of management priorities rather than from its actual impact on funding levels. The rapid reversal of trends induced by the resource allocation methodology during the year after it was suspended may also indicate that the methodology fostered practice patterns that were not consistent with clinicians' best clinical judgment or preferred practice patterns.

Both VA and non-VA data suggest that DRG-based budgeting can have a profound effect on patterns of psychiatric care, at least in the short run. Further studies, however, are needed to determine the impact of these changes on the quality and effectiveness of patient care.

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# Have General Hospitals Become Chronic Care Institutions for the Mentally Ill?

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*Objective: Dramatic increases in lengths of stay for general hospital psychiatric patients in New York City in recent years have raised speculation that general hospitals are assuming a large responsibility for care of the chronically mentally ill. This study examines changes in utilization patterns and patient characteristics to assess whether such a trend is occurring. Method: The authors obtained discharge abstract data for all New York City general hospital adult psychiatric patients in 1985 and 1988 as well as utilization data from the public general hospital system for 1977–1989. Three measures of chronicity were chosen: hospital stays longer than 60 days, discharges to long-term care, and three or more admissions per year. Data on psychiatric diagnoses and comorbid diagnoses for chronically ill patients were also reviewed. Results: The mean length of stay of psychiatric patients in general hospitals has increased substantially in recent years and nearly tripled in the public hospitals during 1977–1989. Between 1985 and 1988, citywide increases were due largely to a growing proportion of patients with very long stays. Patients with stays longer than 60 days accounted for 35% of all inpatient days in 1988, compared with 27% in 1985. Patients with chronic illness accounted for half of all days in 1988, compared with 38% in 1985. Conclusions: Although many factors have contributed to these trends, the leading cause has been reimbursement policies favoring short-term inpatient care. Improving accountability for community treatment programs will be the key to redirecting funding priorities and creating more appropriate alternatives for the chronically mentally ill.*

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The continued depopulation of state psychiatric hospitals, inadequate development of community treatment alternatives, and the more recent epidemics of homelessness and drug abuse among the mentally ill have placed unprecedented pressures on general hospital psychiatry. In New York City, as in other urban centers of the United States, media reports of rising utilization rates and lengths of stay in general hospital psychiatric inpatient services (1–4) have led many to wonder if we are witnessing a trend, as described by Talbott (5) more than a decade ago, toward shifting responsibility for care of the chronically mentally ill from state to general hospitals. The present study was undertaken to assess whether such a trend is occurring; if so, what factors led to this development; and what impact this trend, should it exist, has had on the traditional mission of general hospitals to provide short-term acute care.

## METHOD

We examined changes in utilization patterns (census, admissions, occupancy rates, lengths of stay, readmission rates, and discharge disposition) and patient characteristics (psychiatric diagnoses and comorbid diagnoses) in general hospital psychiatric units in New York City over time for evidence of a shift in the locus of care for the chronically mentally ill. Our primary data source was discharge abstract data (principal psychiatric diagnosis, comorbid diagnoses, discharge disposition, and length of stay) for all New York City general hospital discharges of adult (18 years old or older) psychiatric patients. We obtained these data from the New York Statewide Planning and Research Cooperative System for the most recent year (fiscal year 1988, covering July 1, 1987, to June 30, 1988)

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and the earliest year (calendar year 1985) available. The database included 29,694 discharges in 1988 and 30,382 discharges in 1985. To review longer-term trends, we obtained general utilization data for 1977–1989 from the public hospital system, which currently treats more than half of the city's general hospital psychiatric patients. Data on readmission rates were taken from a study of 1987 and 1988 Statewide Planning and Research Cooperative System data conducted by the New York State Office of Mental Health and from a public hospital study of readmissions during 1986, which was based on billing data submitted to the Statewide Planning and Research Cooperative System. Changes between 1985 and 1988 were tested for statistical significance using chi-square tests for changes in proportions and t tests for changes in mean lengths of stay.

In addition to describing changes in the overall patient population, we were interested in identifying the incidence of chronic mental illness and the utilization behavior and characteristics of chronically ill patients. This presented a number of definitional and data limitation problems. For one, attempts at defining chronic mental illness usually have focused on patients in long-term-care settings, not general hospitals. Second, some of the more obvious indicators of chronicity (e.g., level of functioning, history of psychiatric treatment) were either not available or only partially available in the Statewide Planning and Research Cooperative System. As a result, we selected from the available data potential measures of chronic mental illness that we felt best reflected the three dimensions of chronicity discussed in the literature (6), namely, severity of diagnosis, major functional impairment, and extended duration of treatment.

We first grouped patients by three types of utilization behavior suggestive of chronic mental illness: discharge to long-term care, extended hospital stays, and recidivism. Discharges to long-term care, as reported in the Statewide Planning and Research Cooperative System database, include only patients discharged to selected long-term-care facilities (state psychiatric hospitals, nursing homes, and health-related facilities) and exclude patients discharged to residential and structured treatment programs (e.g., community residences, partial hospitalization, and continuing treatment programs). In addition, the accuracy of hospital discharge coding has not been established, and many patients requiring long-term care cannot be accommodated because of bed shortages. As a result, this indicator was considered only a partial measure of the need for long-term care. Our second measure was hospital stays longer than 60 days, which we presumed were evidence of severity of illness and difficulty in finding aftercare placements. The third measure, recidivism, included patients with three or more admissions per year. We believe that this indicator was also underreported because only readmissions to the same hospital could be identified in available databases. Once we established a subgroup of patients meeting these utilization criteria, we then tested the relationship of the utilization behaviors to each other and to selected psychiatric diagnoses commonly associated with chronicity (schizophrenia, organic brain disorders, and comorbid medical and substance abuse), using chi-square tests, to determine if the overall mix of factors suggested the presence of chronic mental illness.

## RESULTS

### *Utilization Patterns*

Citywide utilization data before 1985 were not available because data sources other than the Statewide Planning and Research Cooperative System generally include patients hospitalized for alcohol and substance abuse among psychiatric patients. However, data for adult psychiatric inpatients in the public hospital system during 1977–1989 revealed major changes in utilization patterns. Although the mean daily census more than doubled during the 13-year period (from 581 to 1,189), admissions actually fell by 19% (from 20,309 to 16,445), mean length of stay nearly tripled (from 10.5 days to 28.4 days), and occupancy rates rose from 83% to 104% (data from the New York City Health and Hospitals Corporation). Citywide utilization data for 1985 and 1988 showed similar trends: while discharges dropped by 2%, mean length of stay increased by 13% (27.4±32.7 versus 24.2±28.0 days; $t=13.3$, $df=58,656$, $p<0.0001$). In addition, citywide occupancy rates have increased substantially, from 85% in 1975 to 97% by the end of 1988 (7, 8).

As shown in table 1, the citywide increase in mean length of stay during 1985–1988 was not evenly distributed over all patients. Rather, it was due to significant shifts in the distribution of patients by length-of-stay category. Most strikingly, utilization by patients with stays longer than 60 days increased significantly, while that of patients with stays shorter than 21 days declined. It was also notable that by 1988, discharges with stays longer than 60 days accounted for more than one-third of all psychiatric inpatient days. Although the concentration of long-stay patients was greater in the public system (10% of the discharges and 39% of the hospital days in 1988), it was substantial among private hospitals as well (9% of discharges and 31% of hospital days).

Discharges to long-term-care facilities increased from 6% to 10% of discharges and from 10% to 15% of days between 1985 and 1988. The increase was mostly due to a doubling of the number of patients discharged to state psychiatric hospitals (from 1,004 to 2,110), while the number of patients discharged to other facilities increased by 8% (from 872 to 945). These differences were found to be significant at $p<0.0001$.

Studies of readmission rates have been limited by the lack of a universal patient identifier in the Statewide

**TABLE 1. Discharges and Days of Hospitalization for Psychiatric Patients in New York City General Hospitals, 1985 and 1988**

| | Discharges | | | | Days of Hospitalization | | | |
|---|---|---|---|---|---|---|---|---|
| | 1985 (N=30,382) | | 1988 (N=29,694) | | 1985 (N=734,798) | | 1988 (N=814,455) | |
| Length of Stay (days)[a] | N | % | N | % | N | % | N | % |
| 1–20 | 17,684 | 58.2 | 15,944 | 53.7 | 174,523 | 23.8 | 154,226 | 18.9 |
| 21–40 | 7,828 | 25.8 | 7,948 | 26.8 | 222,366 | 30.3 | 227,797 | 28.0 |
| 41–60 | 2,842 | 9.4 | 2,990 | 10.0 | 140,215 | 19.1 | 147,352 | 18.1 |
| More than 60 | 2,028 | 6.7 | 2,812 | 9.5 | 197,694 | 26.9 | 285,080 | 35.0 |

[a] All differences in percentages greater than 2% were significant at $p<0.0001$ according to chi-square tests.

Planning and Research Cooperative System database to track cross-hospital readmissions. However, the state and the public hospital system have conducted studies of patients readmitted to the same facility. The state study (unpublished 1990 study by D. Marek) found that the percentage of New York City general hospital psychiatric discharges with two or more admissions within 1 year rose from 24.2% in 1987 to 26.4% in 1988, a 9% increase. Rates for the public hospital system were somewhat higher (25.4% in 1987 and 27.6% in 1988) but showed the same rate of increase. The public hospital system study (unpublished 1987 study of L.K. Garcia) showed that 7% of patients in 1986 had three or more admissions within 1 year and accounted for 19% of all patient days.

### *Patient Characteristics*

A review of discharges and days by major diagnostic categories (schizophrenia, organic disorders, affective psychoses, and nonpsychoses) for 1985 and 1988 showed that patients with organic disorders rose from 6% to 9% of discharges and from 8% to 10% of days between 1985 and 1988. Patients with psychoses (schizophrenia and affective psychoses) dropped from 75% to 72% of discharges and from 79% to 77% of days. Nonpsychotic patients represented 19% of discharges and 13% of days in both years. All changes in percentages were significant at $p<0.0001$.

The rate of comorbid medical and substance abuse diagnoses increased between 1985 and 1988. Although comorbid substance abuse is known to be underreported in discharge abstracts (largely because it impedes aftercare placement efforts and, by regulation, must be confirmed through testing within 30 days of discharge), the relative increase shown during the study period (from 16% of discharges in 1985 to 23% in fiscal year 1988, significant at $p<0.0001$) appears to reflect trends reported by clinicians. The incidence of comorbid medical diagnoses rose from 39% to 43% (also significant at $p<0.0001$).

### *Incidence of Chronic Mental Illness*

As we have already noted, we were interested in estimating the incidence of chronic mental illness among the patient population. As shown in table 2, there was a strong relationship between the utilization behaviors suggestive of chronic mental illness and psychiatric diagnoses and comorbid diagnoses associated with chronicity.

The rate of schizophrenia and organic brain disorders among patients with utilization-related chronicity indicators (multiple admissions were excluded because of the lack of comparability with the citywide data) was 63%, compared with 43% for patients without such indicators. The rate of comorbid medical diagnoses was 55% for chronically ill patients versus 42% for patients without indicators of chronicity. A review of the most frequent medical diagnoses for these patients revealed that most were not of a serious enough nature to have been the primary cause of excessive lengths of stay. Rather, they were evidence of general physical neglect or conditions often seen among the homeless population in the city (e.g., foot and leg infections, anemia, dehydration, hypertension, alcohol-induced convulsions, urinary tract infections, and dental caries). The rate of substance abuse was considerably lower for the chronically ill groups. However, this could be due to coding practices because patients hospitalized for longer than 60 days are not likely to show evidence of drug use and patients successfully placed in long-term-care facilities are less likely to be reported as drug or alcohol users.

We also found significant relationships among the three utilization-related chronicity indicators. Long-stay patients were more likely than shorter-stay patients to be discharged to long-term care (20% versus 9%, $p<0.0001$) and to have three or more admissions per year (28% versus 17%, $p<0.0001$).

## DISCUSSION

During the past decade, major changes in utilization patterns and patient characteristics have occurred in general hospital psychiatry in New York City. Lengths of stay have increased, largely due to a growing proportion of patients with very long stays; admissions are down among patients with stays shorter than 3 weeks; more patients have medical and substance abuse complications; and recidivism rates appear to be rising as well.

These findings present considerable evidence of a

**TABLE 2. Relation of Primary and Comorbid Diagnoses to Chronicity for Discharges of Psychiatric Patients in New York City General Hospitals, 1988[a]**

| | Long-Term Care (N=3,055) | | Not Long-Term Care (N=26,639) | | Long Stay[b] (N=2,812) | | Not Long Stay[b] (N=26,882) | | Multiple Admissions[c] (N=2,961) | | No Multiple Admissions[c] (N=13,169) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diagnosis | N | % | N | % | N | % | N | % | N | % | N | % |
| Primary diagnoses | | | | | | | | | | | | |
| Schizophrenia | 1,536 | 50 | 9,308 | 35 | 1,363 | 48 | 9,481 | 35 | 2,024 | 68 | 6,104 | 46 |
| Organic disorder | 463 | 15 | 2,103 | 8 | 356 | 13 | 2,210 | 8 | 92 | 3 | 504 | 4 |
| Total for schizophrenia and organic disorder | 1,999 | 65 | 11,411 | 43 | 1,719 | 61 | 11,691 | 43 | 2,116 | 71 | 6,608 | 50 |
| Comorbid diagnoses[d] | | | | | | | | | | | | |
| Medical | 1,635 | 54 | 11,111 | 42 | 1,607 | 57 | 11,139 | 41 | —[e] | | —[e] | |
| Substance abuse | 526 | 17 | 6,393 | 24 | 428 | 15 | 6,469 | 24 | —[e] | | —[e] | |

[a] All differences greater than 1% were significant at $p<0.0001$ according to chi-square tests for proportions.

[b] Longer than 60 days.

[c] Three or more admissions per year. Data on multiple admissions were based on a 1986 study of public hospital admissions.

[d] Discharges with both medical and substance abuse comorbid diagnoses were included in both categories.

[e] Data on comorbid diagnoses were not available for these patients.

growing trend toward the use of general hospital psychiatric units in New York City to treat chronically ill patients. By fiscal year 1988, 35% of all days in these units were devoted to patients with long stays (stays longer than 60 days, averaging 101.4 days per admission). Another 7% of days were attributable to patients with shorter stays (60 days or fewer) who were discharged to long-term-care facilities. In the public hospital system, patients admitted three or more times per year (excluding long-stay patients and those discharged to long-term-care facilities) accounted for an additional 8% of days. Altogether, these three groups of patients, all of whom had multiple characteristics of chronic mental illness, were conservatively estimated to account for half of psychiatric days in the city's general hospitals in fiscal year 1988, up from an estimated 38% in 1985. (We believe that the estimate is conservative because the number of patients discharged to long-term care and those readmitted three or more times per year are understated due to limitations of the databases.) There is further evidence (high occupancy rates and reduction in shorter-stay admissions) to suggest that this growing presence of chronically ill patients may be denying access to other patients in need of acute care.

### *Environmental Factors*

The environmental forces—trends in the greater mental health service community, reimbursement policies, and urban problems—that have contributed to these developments are a familiar litany to those involved in treatment of the chronically mentally ill (9). As is true nationally, there has been a major shift in the location of psychiatric treatment in New York City during the past three decades. From 1965 to 1990, the state hospital census in the city dropped by 74%, from 14,970 to 3,920. The statewide census fell at an even greater rate—82%—from 84,859 to 15,207 (10). As a means of achieving the reduction in capacity, state hospitals have introduced more restrictive admission criteria that exclude patients with organic brain disorders, medical complications, and alcohol and drug addiction.

Nursing homes, which have been a major resource nationally for the chronically mentally ill since deinstitutionalization (6, 11), are far less available in New York City than elsewhere. Because New York State has strictly regulated the growth of the number of nursing home beds, the number of beds per 1,000 people aged 75 and older in New York City has declined from 105.3 in 1977 to 90.8 in 1987 (compared with 129.2 beds nationally) (7). The growing proportion of the city's population in this age group (projected to increase by more than 30% during the next 20 years [7]); New York State's reimbursement system for long-term care, which assigns relatively low cost intensity weights to psychiatric diagnoses; and recent federal restrictions on payment for psychiatric treatment in nursing homes have all placed the mentally ill at a disadvantage in the competition for scarce nursing home beds.

New York City faces a severe shortage of community treatment programs, perhaps intensified by its position as a major migration center for the chronically mentally ill. According to the New York City Department of Mental Health, during 1980–1989 (the longest period for which citywide outpatient data were available), outpatient visits in New York City increased by 42%, from 1,865,000 to 2,640,000. However, three-quarters of the growth in outpatient activity was financed by federal and state grant programs (e.g., Community Support Services), but third-party-reimbursed visits increased by only 12%, from 1,691,000 to 1,890,000 (data from the New York City Department of Mental Health). In 1989, there were only 2,528 community residence beds for the mentally ill in New York City (data from the New York State Office of Mental Health).

As is widely acknowledged (12, 13), federal reimbursement policies have been a key force propelling the growth and redirection of general hospital psychiatry. Both Medicare and Medicaid, which together reimbursed 75% of general hospital psychiatric days in New York City during fiscal year 1988, set strict limits on payment for care in psychiatric hospitals. Medicare, which serves geriatric and disabled patients, pays for up to 60 days per stay in psychiatric hospitals but places no limit on stays in general hospitals. Moreover, Medicare has a lifetime limit on benefits. In practice, many of the chronically mentally ill exhaust their lifetime Medicare benefits and become eligible for Medicaid. Medicaid disallows payment for psychiatric hospital patients (with the exception of persons older than 64 and younger than 22 years of age). These policies, originally intended to promote deinstitutionalization, now provide states with powerful incentives to shift inpatient care from state psychiatric hospitals to general hospitals. In addition, Medicare and Medicaid set low rates for outpatient services, while inpatient rates are tied to actual costs. New York State, for example, has had a rate limit of $60 per hospital-based outpatient visit in effect since 1981 (the rate was $55 for the previous 5 years) for non-Medicare payers. Studies have shown that the actual average cost of hospital-based mental health outpatient programs in New York City is more than double the reimbursement rate (unpublished 1989 studies of S.A. Salit). Moreover, this rate applies equally to all mental health programs and all activities within programs despite major variations in treatment modalities and costs. (Beginning in April 1991, New York State began to address this problem by increasing rates for partial hospitalization and continuing treatment programs. However, due to the state's fiscal difficulties, not all of these rates apply to hospital-based programs.)

In more recent years, the epidemics of homelessness and drug abuse have vastly complicated treatment of the chronically mentally ill in the city. During the 1960s through the early 1970s, when deinstitutionalization was at its peak in New York State, thousands of mental patients found shelter in New York City's single-room occupancy hotels. However, from the late 1970s through the 1980s, a real estate boom in the city eliminated this housing: an estimated 110,000 units of single-room occupancy housing, representing 87% of the total supply, were lost in New York City during 1970 to 1982 (14). Cutbacks in federal housing subsidies during the same period further reduced the overall availability of low-income housing. In 1989, city housing officials estimated the vacancy rate for low-rent apartments at less than 1%, the waiting period for public housing at 10–20 years, and the number of homeless persons at 70,000–80,000 (36,000 of whom were in city shelters) (15). Studies have estimated that one-third of homeless persons in the city, as well as nationally, have serious mental illness (13, 16, 17). Although reliable data on the dimension of the drug problem among the chronically mentally ill in the city are not available, a 1990 public hospital survey (April 1990 data from the Office of Mental Hygiene, New York City Health and Hospitals Corporation) found that one-third of patients treated in psychiatric emergency rooms were believed to be frequent drug users.

## *Public Policy Implications*

Further research is needed to understand the treatment and placement needs of chronically ill patients in the city's general hospitals. Some observers believe that housing alone would prevent a portion of these hospitalizations. They point out that during the 1970s, when single-room occupancy hotels were available in the city, general hospital utilization rates were far below current levels. Others speculate that a second wave of deinstitutionalization which began in the 1980s in New York State released a much less functional group of patients who perhaps cannot maintain themselves in the community. Yet another more recently emerging group are young, never-institutionalized substance abusers for whom treatment approaches are still in the experimental stages.

The second major challenge is to redirect federal and state reimbursement policies. At the core of these policies is a profound skepticism about the effectiveness of community treatment programs, which have been widely criticized for "skimming the chronic population of the more motivated and functional patients" (18) or otherwise failing to engage the most seriously ill (19). Finding ways of targeting these programs to the seriously ill, holding them accountable for achieving outcomes, and demonstrating their cost effectiveness will be the key to overcoming this skepticism. A potential tool for achieving this—use of computerized payment databases—has shown promise in New York State. New York's Medicaid payment system recently was used to identify the most frequent users of inpatient and emergency services in New York City, assign them case managers, and monitor their subsequent hospitalizations and compliance with outpatient treatment. These systems also enable policy makers to understand the economic tradeoffs involved in substituting community care for hospitalization. This, in itself, may present a compelling case for shifting funding priorities (e.g., the average cost per admission for "long-stay" general hospital patients in New York City in 1988 was $43,000).

In summary, once the treatment needs of chronically mentally ill patients in general hospitals are better defined and techniques for targeting and evaluating community services are improved, an appropriate mix of services and reimbursement structures to support their development can be devised.

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# Relationships Between Requests for Psychiatric Consultations and Psychiatric Diagnoses in Long-Term-Care Facilities

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Objective: *The authors' objective was to investigate reasons for referral of elderly nursing home residents for psychiatric consultation and the relationship of these reasons for referral to psychiatric diagnoses.* Method: *They examined 197 nursing home residents consecutively referred to a consulting team in a university-affiliated mental health center. These patients represented all patients evaluated by the consulting team at six nursing homes over a 2-year period (Sept. 1, 1984, through Aug. 30, 1986).* Results: *Reasons for referral were diverse but fell into seven broad clusters: behavioral problems; mood-related problems; consultations requested by involuntary treatment services, patients, physicians, or other referring agencies; psychotic features; physical signs; impaired activities of daily living; and other. Behavioral problems were most commonly cited and tended to be associated with dementia diagnoses. Mood-related reasons for referral were most strongly associated with diagnoses of affective disorders, and diagnoses of schizophrenia and adjustment disorder were each associated with two or more reasons for referral. However, reasons for referral were distributed widely across diagnostic groups and were relatively weak predictors of diagnoses.* Conclusions: *The results illustrate the variety of problems for which nursing home staff are willing to seek psychiatric consultation but emphasize the need for professional psychiatric evaluation to establish a diagnostic base on which treatment interventions can be built.*

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Research on psychiatric aspects of nursing home care is still scarce (1). Most of the quantitative studies performed have focused on establishing the prevalence of mental illness among nursing home residents (2) and on the applicability of diagnostic categories to the disorders found in this population. A study reported in 1976 (3) found that 85% of 74 patients in two skilled nursing facilities had substantial psychiatric disorders and that almost two-thirds of these disorders had not been diagnosed. A more recent investigation (4) reported similar results.

When nursing home staff seek psychiatric consultation, their requests are commonly framed not in terms of psychiatric diagnoses but in terms of maladaptive behaviors or "target" symptoms that have been troublesome to the patient, other residents, or the staff of the facility. These reasons for referral bear an uncertain relationship to psychiatric diagnoses (5, 6) and are subject to bias of several kinds. Strong emotional responses to patients and hidden conflicts among staff members are some of the most common of these biases.

Our clinical work in a variety of nursing home settings suggested to us that appraisals by nursing home staff and psychiatric consultants frequently diverge broadly. Very different ways of understanding and assessing patients might impede successful consultation and even hinder development of the collaboration between psychiatrists and nursing homes that could enhance the care of mentally impaired, dependent patients (7, 8). Our aim in this paper, therefore, was to examine the relationships between reasons for referral and diagnoses and thereby to make explicit the degree of congruence (or divergence) between nursing home staff, who draw on a descriptive frame of reference, and physicians, who have a syndromal and diagnostic frame of reference.

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**TABLE 1. Characteristics of Six Nursing Homes Given Psychiatric Consultations Over a 2-Year Period**

| Facility | Type of Facility | Description | Number of Beds | Number of Referrals |
|---|---|---|---|---|
| 1 | Skilled nursing facility | Inner city, high percentage of minority patients, exceptional staff sensitivity at all levels | 177 | 62 |
| 2 | Skilled nursing facility/ intermediate care facility | Near major hospitals, patients mainly Caucasian, traditional medical nursing model | 178 | 30 |
| 3 | Skilled nursing facility/ intermediate care facility | Sponsored by church, middle-class Caucasian residents, traditional nursing model, low staff turnover, exemplary physical care | 211 | 14 |
| 4 | Intermediate care facility | Near county hospital, patients mainly male, long-term alcoholics | 37 | 11 |
| 5 | Skilled nursing facility/ intermediate care facility | Many younger, chronically psychotic patients; chronic financial and administrative problems, high staff turnover, good physical care | 250 | 62 |
| 6 | Skilled nursing facility/ intermediate care facility | Chronic financial problems, organizationally weak, staff not psychologically minded, physical care marginal at times | 115 | 18 |

We report here the results of a descriptive cross-sectional study comparing the reasons for referral for psychiatric consultation and the diagnoses made by the consulting team. We present data on and evaluate relationships among characteristics of the nursing homes, demographic descriptions of patients, and clinical variables.

## METHOD

The Residential Care Unit of Harborview Community Mental Health Center is a multidisciplinary team comprising a psychiatrist, a psychiatric nurse, and geriatric mental health specialists. It provides on-site psychiatric services to nursing homes in both consultative and direct care modes of practice. The study group, 197 patients consecutively referred for consultation, represents all patients evaluated at six nursing homes over a 2-year period (Sept. 1, 1984, through Aug. 30, 1986). Table 1 provides descriptions of the nursing homes, all of which had received psychiatric services on a contractual basis from the Residential Care Unit over several years before the initiation of this study.

Diagnostic assessment of patients was performed by one of two psychiatrists experienced in the care of the elderly (J.P.L. and S.B.), using *DSM-III* criteria. Where multiple diagnoses were made, only the diagnosis judged responsible for the presenting clinical problem (primary diagnosis) was used in the analysis.

Reasons for referral were recorded at the time of referral by using the actual wording of the referring person. Several reasons for each referral were often cited. The large number of reasons for referral elicited (N=312) was reduced, for use in data analysis, by sorting them into seven thematic clusters (appendix 1). This classificatory method has been used in other, similarly naturalistic investigations (9) and was readily accomplished by consensus among the five clinicians. Each one of the reasons for referral was assigned to only one of the seven clusters.

Pearson product-moment correlation coefficients were computed for patient-related variables (demographic characteristics and psychiatric history) and reasons for referral. Stepwise logistic regression (10) was used to examine the relationship between diagnoses and reasons for referral. For this analysis, outcome (psychiatric diagnosis) was coded as a binary variable. For example, a final diagnosis (e.g., dementia) was coded 1 if present and 0 if absent. Because only the primary diagnosis for each patient was considered, this procedure divided the 197 patients into two groups, serially: demented and nondemented, schizophrenic and nonschizophrenic, and so forth. With reasons for referral constituting the independent variables, a stepwise logistic regression analysis was performed on each of the major disorders found in the study group. Statistical significance for inclusion of independent variables in the model was set at $p<0.05$. Significance of independent variables in the regression equation was determined by the likelihood ratio test (10).

## RESULTS

Table 2 presents the characteristics of the subjects and provides a comparison of some of these characteristics with those of patients in Washington State facilities as a whole (11). The mean±SD age of patients in the study group was 74.5±14.2 years, and the majority were Caucasian. The group studied is not an exact reflection of the Washington State profile of long-term-care residents: more patients younger than 75 and more men were referred for consultation than are represented in the state profile. Fifty-eight percent of the patients in the study group were 74 years old or younger, compared with 29% of those in nursing homes in general. The usual preponderance of female residents was not seen in the study group, where men outnumbered women two to one. These differences may reflect the inclusion of two nursing homes specializing in the care of younger, chronically mentally ill persons discharged from state hospitals (facility 1) and older chronically alcoholic men (facility 4); 73 (37%) of the 197 patients in our study group were referred

**TABLE 2. Characteristics of 197 Nursing Home Residents Given Psychiatric Consultations and Nursing Home Residents of Washington State**

| Characteristic | Study Group N | Study Group % | Nursing Home Residents (%)[a] |
|---|---|---|---|
| Age (years) | | | |
| 55 and younger | 10 | 5 | 9 |
| 56–65 | 39 | 20 | 5 |
| 66–74 | 65 | 33 | 15 |
| 75–84 | 51 | 26 | 32 |
| 85 and older | 32 | 16 | 40 |
| Sex | | | |
| Men | 132 | 67 | 30 |
| Women | 65 | 33 | 70 |
| Race | | | |
| Caucasian | 163 | 83 | —[b] |
| Black | 26 | 13 | —[b] |
| Asian | 6 | 3 | —[b] |
| Other | 2 | 1 | —[b] |
| Education | | | |
| 12 years or less | 148 | 75 | —[b] |
| 13 years or more | 49 | 25 | —[b] |
| Marital status | | | |
| Married | 18 | 9 | —[b] |
| Widowed | 85 | 43 | —[b] |
| Divorced | 47 | 24 | —[b] |
| Never married | 31 | 16 | —[b] |
| Single (not otherwise specified) | 16 | 8 | —[b] |
| Previous psychiatric history | | | |
| None | 96 | 49 | —[b] |
| Treated as outpatient | 20 | 10 | —[b] |
| Treated as inpatient | 24 | 12 | —[b] |
| Treated as inpatient and outpatient | 57 | 29 | —[b] |

[a] Source: State of Washington Aging and Adult Services Administration (11).

[b] Data not available.

from these two facilities. An additional factor may be disproportionate referral of male patients because of sex differences in the rate of certain behaviors or heightened staff concern about behavioral problems such as aggressive outbursts when they occur in male patients. These variables cannot be examined in detail on the basis of currently available data. Nearly half of the patients referred had a previous psychiatric history, including 15 (48%) of the 31 patients referred for psychotic features and 21 (30%) of the 69 referred for mood-related problems.

The most common reasons for referral were behavioral problems, cited for 96 (49%) of the 197 patients. Mood-related reasons for referral were given for 69 (35%), psychotic features for 31 (16%), and unexplained or problematic physical signs for 23 (12%) of the patients. Requests for follow-up for an established mental disorder or consultation, with no clinical problem cited, from another clinician were the reasons for referral for 37 (19%) of the patients. Cognitive impairment, functional disabilities (impaired activities of daily living), and adjustment problems were each cited as reasons for referral in fewer than 10% of the patients. The median number of reasons for referral was two, and the mode was one; two or fewer reasons for referral were given for 158 (80%) of the subjects.

No statistically significant correlations were found between reasons for referral and age, education, gender, marital status, or ethnicity.

Four groups of psychiatric diagnoses accounted for 170 (86%) of the patients: 69 (35%) of the patients had dementia, including 36 patients (18%) with primary degenerative disorders, 26 (13%) with mixed types, and seven (3%) with vascular dementias. Major and organic affective disorders and anxiety disorders were found in 38 (19%) of the patients, adjustment disorders in 32 (16%), and schizophrenia or paranoid disorder in 31 (16%). Active substance abuse disorders were diagnosed in 10 (5%) of the patients and delirium or acute confusional states in three (2%). No diagnosis could be made in 14 (7%) of the patients; this includes some individuals with no disorder and some for whom a definitive diagnosis was obscure and had to await longer follow-up.

Correlations between diagnoses and reasons for referral were modest. Statistically significant correlations, both negative, were found for mood-related reasons for referral with dementia ($r=-0.14$, $df=67$, $p<0.05$) and with schizophrenia or paranoid disorders ($r=-0.26$, $df=67$, $p<0.01$). This result suggests that affective complications of dementia and schizophrenia or paranoid disorders may be uncommon in the long-term-care facilities participating in this study. Alternatively, it may mean that affective signs and symptoms are overlooked by staff or not seen as justifying consultation and treatment.

Stepwise logistic regression analysis identified significant reasons for referral predictors for each of the four major diagnostic groups (table 3). For subjects referred for behavioral problems, the odds of having a dementia diagnosis were nearly three times as high as the odds of having another psychiatric diagnosis. The odds that a patient referred for a mood-related problem would receive an affective or anxiety diagnosis were three and a half times the odds of receiving another diagnosis. For diagnoses of adjustment disorder, having more than one reason for referral significantly predicted diagnosis: the odds of having a diagnosis of adjustment disorder were three and a half times higher in patients referred for mood problems or physical signs; the combination markedly increased the odds. The odds of having a diagnosis of schizophrenia or paranoid disorders were higher for patients referred for psychotic features than they were for patients referred for mood-related reasons and behavioral problems.

The results of logistic regression yielded models of prediction of diagnoses from reasons for referral that were generally in the expected directions but not necessarily very powerful. The reasons for this are shown in table 4, which shows the spread of reasons for referral cited by staff for each diagnostic group. Each diagnosis generated a wide array of reasons for referral. For example, although 45 of the 69 patients with

**TABLE 3. Stepwise Logistic Regression Analysis of Associations Between Reasons for Referral for Psychiatric Consultation and Diagnosis for 197 Nursing Home Residents**

| Diagnosis | Significant ($p<0.05$) Predictors | Relative Odds | 95% Confidence Limits | p |
|---|---|---|---|---|
| Dementia | Behavioral problems | 2.8 | 1.5–5.1 | 0.0008 |
| Affective and anxiety disorders | Mood-related problems | 3.6 | 1.7–7.6 | 0.0006 |
| Adjustment disorder | Mood-related problems | 3.6 | 1.6–8.0 | <0.02 |
| | Physical signs | 3.6 | 1.3–9.5 | |
| | Mood-related problems plus physical signs | 12.6 | 2.1–76.4 | |
| Schizophrenia and paranoid disorders | Mood-related problems | 0.1 | 0.04–0.5 | <0.03 |
| | Psychotic features | 4.5 | 1.8–11.3 | |
| | Behavioral problems | 0.4 | 0.2–0.1 | |

**TABLE 4. Relation Between Diagnoses and Reason for Referral for Psychiatric Consultation for 197 Nursing Home Residents**

| | Dementia (N=69) | | Affective and Anxiety Disorders (N=38) | | Adjustment Disorder (N=32) | | Schizophrenia and Paranoid Disorders (N=31) | | Other[b] (N=27) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Reason for Referral[a] | N | % | N | % | N | % | N | % | N | % |
| Behavioral problems | 45 | 65 | 13 | 34 | 13 | 41 | 11 | 36 | 14 | 51 |
| Mood-related problems | 16 | 23 | 23 | 61 | 21 | 66 | 2 | 6 | 7 | 25 |
| Consultation requested | 10 | 15 | 9 | 24 | 5 | 16 | 8 | 26 | 5 | 18 |
| Psychotic features | 7 | 10 | 5 | 13 | 0 | 0 | 14 | 45 | 5 | 19 |
| Physical signs | 6 | 9 | 4 | 11 | 9 | 28 | 1 | 3 | 3 | 11 |
| Impaired activities of daily living | 6 | 9 | 1 | 3 | 4 | 13 | 0 | 0 | 2 | 8 |
| Other[c] | 19 | 27 | 5 | 13 | 8 | 25 | 8 | 26 | 3 | 11 |

[a] There were 312 reasons for referral; each subject could be given more than one reason for referral.
[b] Includes patients with diagnoses of substance abuse and confusional states, patients undiagnosable with available information, and those with no disorder.
[c] Includes clusters for cognitive impairment, adjustment problems, suicidal acts and/or ideation, and unclustered reasons for referral.

a diagnosis of dementia were referred for reasons in the behavioral problems cluster, 20 were referred for mood-related reasons; dementia generated reasons for referral in every other category as well. Of the 38 patients with diagnoses of affective and anxiety disorders, 23 were referred for mood-related reasons. However, many patients in this diagnostic group were referred for behavioral problems and psychotic features and, to a lesser extent, for problems in the remaining clusters. Of the 32 patients with a diagnosis of adjustment disorder, the majority were referred for behavioral problems, but many were also referred for all of the other reasons except psychotic features. Many of the 31 patients with diagnoses of schizophrenia or paranoid disorders were referred not only for psychotic features but for behavioral problems as well. The relatively small group of patients with a diagnosis of substance abuse also had a variety of reasons for referral, most commonly behavioral problems (data not shown; included in other diagnoses).

## DISCUSSION

To our knowledge, this study is the first to offer an examination in detail of the problems for which nursing home staff seek assistance from psychiatric consultants in managing patients and the relationship between behaviors of concern to such staff and psychiatric diagnoses. Several broad conclusions emerge from this analysis. First, nursing home staff members who have experience in working with a consulting team will make referrals for a wide array of problems, including mood changes, confusion, apathy, impaired self-care, and aggressive outbursts. This range speaks to the capacity of many nursing home staff members to make detailed and often subtle observations of their patients and to their willingness to seek advice and assistance when problems arise.

Second, these observations, although often descriptively rich, cannot serve as proxies for psychiatric diagnoses. Relationships between reasons for referral and formal diagnoses, expressed as correlations or as relative odds, indicate that reasons for referral are only modest predictors of diagnoses. Although this finding may come as no surprise to well-trained psychiatrists, it has important implications for psychiatric services planning in this still-isolated and underserved sector of the health care system. It may help to explain the substantial mismatch between psychiatric needs of nursing home patients and the care they receive for their behavioral and emotional problems (12). For example, in the many nursing homes where psychiatric consultation is only minimally available (if at all), staff reports may be the only data on which treatment decisions are based. This, in turn, may foster "shotgun" psychopharmacological interventions that satisfy neither current guidelines for treatment of the mentally ill nor the individual needs of patients. Several sources attest to widespread misuse of psychotropic medication in nursing homes (5, 12, 13).

An additional implication of our results is that psychiatric diagnoses do not substitute for primary information from staff about patient behavior. Diagnostic assessment and detailed staff reports provide complementary, if overlapping, information, and both are necessary for the development of comprehensive treatment plans that will be understood, accepted, and reliably implemented by institutional caregivers, who bear the primary responsibility for long-term care of patients. The realities of being aged, ill, and dependent on others for care create a degree of clinical complexity that is not captured by diagnostic categories but is better conveyed by the varied and impressionistic language used by nursing home staff (appendix 1). Further, not all disturbances for which staff seek assistance from psychiatry can be readily attached to a definite psychiatric diagnosis. In our study group, nearly 10% of the patients were considered incompletely diagnosable on the basis of clinical information available in records and at the bedside.

Our data suggest that the problems for which psychiatric consultations are sought are similar across diagnostic categories and arise from the interaction of a broad range of emotional, cognitive, behavioral, and illness-related factors in the context of caregiving relationships. This contrasts with the observation that behavioral problems, especially socially disruptive and aggressive acts, markedly outweigh all others that lead to referral (9). Although behavioral problems were a major source of reasons for referral, accounting for nearly half of all patients referred (table 4), mood-related problems led to referrals for one-third of the patients. Furthermore, new-onset psychiatric disorders complicating dementia and chronic medical illness are not easily distinguished from conventional chronic mental illnesses by the problems they present for caregivers. According to our findings, diagnoses per se do not appear to be an adequate basis for segregating elderly nursing home patients who are chronically mentally ill into diagnostically defined facilities.

Finally, the observation that nearly half of the patients had a previous psychiatric history serves as a reminder of the persistently disabling effects of severe mental illness even in this era of active pharmacotherapy and points to the role of the nursing home in providing continuing care of the chronically mentally ill (14).

Nursing homes serve a vital function in the health services system, caring for patients who have a wide variety of chronic disabilities requiring assistance. The number of patients in nursing homes will continue to grow in response to demographic pressures in the population, particularly the rapid increase in the proportion of the very old (15). The demand for psychiatric services for this population is expected at least to keep pace. The complexity of problems encountered in the unique clinical environment of the nursing home is likely to frustrate or intimidate psychiatrists who do not have training in this setting and to contribute to continuing difficulties in supplying the need for services in the long-term-care setting. Substantial revisions of training to include exposure to the patients and staff in nursing homes are essential if psychiatrists are to be prepared to meet this demand.

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**APPENDIX 1. Reasons for Referral for Psychiatric Consultation in Six Nursing Homes: Thematic Clusters and Their Components**

A. Behavioral problems
   1. Impeding care: inappropriate, bizarre, disinhibited, bothersome, demanding, wandering, intrusive, fecal soiling, smearing, wants to leave nursing home, refuses care, refuses medication, dependent, refuses food and/or drink, smoking problem, problem not otherwise specified
   2. With agitation: cerebrovascular accident, uncontrollable, agitation not otherwise specified
   3. With hostility: threats and/or acts of violence, combative, angry, irritable, explosive, racist remarks, abu-

sive, history of hostility, unpredictable, escalating anger
4. With intrusive vocalization: yelling, screaming, cursing, complaining, moaning
5. With apathy, withdrawal: seclusive, reclusive, unmotivated

B. Mood-related problems
   1. Depression
      a. Crying, hopeless, helpless, emotional lability
      b. Related to loss of speech, blindness, renal failure, amputation, physical deterioration
      c. Related to nursing home placement
      d. History of depression, bipolar affective disorder
      e. Not otherwise specified
      f. Grief and/or bereavement reaction secondary to death of spouse, other losses, or adjustment to physical illnesses
   2. Anxiety
      a. Related to nursing home placement
      b. Related to renal failure
      c. Not otherwise specified
   3. Suicidal act and/or ideation: at risk of suicide, talks of suicide, suicide attempt, self-destructive behavior not otherwise specified

C. Consultation requested by involuntary treatment services, patient, physician, or other referring agency

D. Psychotic features
   1. Symptomatic: hallucinations, delusions, paranoid attitude
   2. History of schizophrenia, paranoia, manic-depressive psychosis, psychosis not otherwise specified
   3. Deterioration in level of psychosis

E. Physical signs: insomnia, weight loss, poor appetite, incontinence, falling, failure to thrive, tardive dyskinesia

F. Impaired activities of daily living: refuses activities, poor self-care

G. Other: delirium, confusion, wishes to leave nursing home, failure to thrive

# New York Under the *Rivers* Decision: An Epidemiologic Study of Drug Treatment Refusal

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*Objective: To determine the characteristics of cases of drug treatment refusal under the Rivers decision, which mandated court adjudication of such cases, the authors made a retrospective study of all applications for court review during 1 year in New York State inpatient facilities. Method: Sociodemographic and clinical characteristics of these 473 cases were compared with those of the 41,535 cases during the same period in which no court review was requested. Results: A 1% prevalence of applications requesting court review for nonemergency administration of medication over objection was found. The patients who refused medication were more likely than the comparison patients to have a crime-associated commitment status, a diagnosis of schizophrenia, and fewer previous hospital days, and they were more likely to be discharged. Medication refusers for whom applications for court review were submitted had relatively longer hospitalizations than the rest of the patients. Almost one-third of the applications submitted were withdrawn before court hearings, yielding a 0.7% prevalence of court-reviewed applications. Ninety-two percent of these applications for medication over objection were approved with virtually no change in the requested orders. Conclusions: The study findings demonstrate that a front-end judicial determination of competency to refuse medication results in a time-consuming procedure which fails to ensure real due process or provide individualized alternative treatment. A two-tier system with in-house clinical review preceding judicial review is proposed to remedy the deficiencies of the current system.*

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Over the past decade, the right of psychiatric inpatients to refuse treatment, particularly psychotropic medications, has continued to be the subject of heated debate in both legal and clinical arenas. Before the late 1970s, involuntary administration of these medications was considered the prerogative of the treating psychiatrist by virtue of the legal authority conferred by the involuntary commitment laws. However, as the scope of involuntary commitment was narrowed by patients' civil rights determinations, this presumed clinical authority was brought into question. A series of court decisions, such as *Rennie v. Klein*, *Rogers v. Okin*, and *Rivers v. Katz*, ensued, and these upheld psychiatric patients' First, Eighth, and Fourteenth Amendment rights to refuse involuntary medication, regardless of commitment status, at least until due process procedures are completed.

Due process procedures generally fall into two categories, which Appelbaum (1) has described and labeled "rights-driven" and "treatment-driven." Rights-driven approaches take the form of court adjudication programs aimed at determining the patient's mental competence to decide whether to accept medication. In these programs, the adequacy and appropriateness of the proposed medication regimen have generally been a secondary issue. In contrast, treatment-driven approaches have relied on clinical review (usually in-house), which has been more focused on the appropriateness of the proposed medication regimen for the patient's clinical state. This approach pays relatively little formal attention to the issue of competency, which is considered to be a judicial determination.

An attempt to reconcile these two divergent due process approaches to patients' refusal of medication was embodied in the *Rivers v. Katz* decision (2) in New York State in 1986. Before the decision, a treatment-driven procedure involving a series of clinical reviews by both in-house and consultant psychiatrists was used as the basis for an administrative decision regarding involuntary medication. In the *Rivers* decision, the court held

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that the patient's constitutional right to self-determination required a formal court hearing to determine the question of competency to refuse treatment before involuntary treatment could be administered. However, the court also asserted its right to rule on the appropriateness of the proposed medication regimen itself (*Rivers* decision, section II-B, paragraph 4), thus inserting a judicial presence into the treatment process, beyond the issue of competency. In this decision, for the first time, a synthesis of the rights-driven and treatment-driven approaches was attempted.

This report presents the results of an epidemiologic study of the first year of experience under the *Rivers* ruling in which data from all New York State Office of Mental Health adult psychiatric centers were examined. The study was undertaken to determine the extent to which this decision has resulted in a merging of the two approaches and to estimate the benefits and costs of this system so as to provide information for further refinement of the process.

## METHOD

Following the *Rivers* decision by the New York State Court of Appeals, the New York State Office of Mental Health's Office of Counsel in conjunction with the Clinical Deputy Commissioner's Office developed a procedure for processing applications for treatment over objection, which was implemented in July 1986. Using information from this process, we conducted a 1-year survey (Nov. 1, 1986, through Oct. 31, 1987) of all New York State adult psychiatric (N=22) and forensic (N=3) facilities to determine the number of such applications for court review and the administrative time factors and decisions related to the court review. In the study year, 473 patients had 481 hospital admissions during which they were the subjects of 499 applications. Of these patients, 95% (N=451) were the subjects of single applications, 4% (N=20) were the subjects of two applications each, and the remaining two patients had three and five applications, respectively, made on their behalf.

After the initial survey, three records were obtained for each subject of an application: 1) the physician's request for treatment over objection, 2) the final order of the court, and 3) pertinent medication administration records. Additional computerized records related to sociodemographic and discharge data for all patient episodes in the study year throughout the system were obtained from a centralized database so as to calculate the prevalence of refusal of medication and to compare refusers who were the subjects of court applications with all other patients.

The physician's request for treatment over objection is a semistructured questionnaire that collects the following clinical information relevant to the issue of the patient's current drug treatment: past history, diagnosis, clinical course, expected benefits and risks of drug treatment, patient's capacity to make an informed decision and to object to treatment, and likelihood of dangerousness. The procedure for requesting court review and its origin were described in an earlier report (3).

For the present report we examined the prevalence, temporal factors, seven sociodemographic and clinical factors, and treatment outcome of cases in which patients who refused medication became the subjects of applications for court review. To characterize the temporal pattern related to the processing of applications, we determined the time to refusal (from the date of admission to the date of the application for medication over objection) and time to action (from the date of the application to the date of the court review or withdrawal of the application). The patients' most recent *DSM-III* axis I diagnoses were grouped in four categories: schizophrenia, affective disorders, atypical psychosis, and organic/other. Patients were classified as having an acute disorder if there had been fewer than three previous episodes or fewer than 730 days of previous hospitalization. Discharge status was categorized as 1) discharge with or without follow-up referral to an outpatient service, 2) transfer, 3) death, or 4) continuation of inpatient status. Length of stay was computed from the date of admission to the date of discharge or Oct. 31, 1988 (1 year from the end of the study interval), allowing 1 year of follow-up for all cases.

To compensate for the large size of the comparison group (more than 41,000 patients), goodness-of-fit chi-square procedures (4) were used. Specifically, since the comparison group was large, the proportions in each category were viewed as "true" values. The goodness-of-fit test determined whether the proportions in the refusers' group were equal to these "true" values.

## RESULTS

During the 1-year study period, 481 admissions involved applications for involuntary administration of medication, representing approximately 1% of all admissions (N=49,408).

In the comparison of patients for whom applications for court review were made (N=473) with those for whom no court review was requested (N=41,535), several significant differences emerged. The patients who refused medication were more likely to be 30–59 years of age ($\chi^2$=66.94, df=3, p<0.0001), to have been admitted involuntarily or by criminal commitment ($\chi^2$=190.21, df=2, p<0.0001), to be designated as acutely ill ($\chi^2$=10.42, df=1, p<0.0001), to have a diagnosis of major psychosis ($\chi^2$=86.83, df=3, p<0.0001), and to have been hospitalized for 91 days to 2 years ($\chi^2$=465.60, df=6, p<0.0001). One year after the end of the study year, significantly more refusers had been discharged (71% versus 61%; $\chi^2$=38.00, df=4, p<0.005), but nonrefusers who were discharged were three times more likely to have been discharged within 90 days of admission ($\chi^2$=241.60, df=1, p<0.0001). The highest rate of refusal of medication occurred among patients on criminal commitment status and among those hospitalized for 6 months to 1 year (both groups had a refusal rate of 3%).

The mean±SD time from admission to refusal of medication was 461±1640 days (range=0–14,607 days; median=63 days), indicating a very skewed time pattern. Seven admissions dating back to the 1950s explain the upper outliers, while 75% of the applications occurred within 7 months of admission. The time to action ranged from 1 to 547 days, with the majority (58%) of the 499 cases being resolved within 1 month of the application. Another 25% were resolved in 1–2 months, 10% required up to 90 days, and the remaining 6% took 91–547 days.

Nearly one-third (N=141) of the applications were withdrawn before court review. Unfortunately, the reasons for withdrawal could not be ascertained from the records reviewed for this study. The mean±SD time to action was somewhat longer for the applications that were court reviewed than for the applications that were withdrawn (38.3±40.4 versus 33.4±49.9 days; t=0.85, df=210.4, n.s.). Most long delays occurred among the court-reviewed cases; however, these delays occurred for only 6% (N=30) of the applications. Thus, the time to process applications did not provide an adequate explanation for withdrawal.

The 135 patients for whom applications were withdrawn were twice as likely as the 338 patients for whom applications underwent court review to be discharged without follow-up (50%, N=68, versus 26%, N=90; $\chi^2$=28.19, df=4, p<0.0001), and they had a higher proportion of shorter current hospital stays (1–180 days): 55% (N=75), compared with 34% (N=116) in the court-reviewed group ($\chi^2$=32.71, df=5, p<0.0001). The discharged subjects of withdrawn applications (N=107) had a significantly shorter mean±SD hospital stay than did those of court-reviewed applications (N=222) (200±189 versus 267±228 days; t=2.80, df=249, p<0.01). Hospital stays of less than 90 days occurred three times more frequently for patients whose applications were withdrawn (29%, N=40) than for patients whose applications were reviewed by the court (9%, N=32), regardless of differences in age, legal status, chronicity, and diagnosis.

Of the 499 applications for court review, 358 (72%) were reviewed by the courts. The physician's request for involuntary medication was approved by the court on the initial request in 91% (N=326) of the cases. Subsequently, five of the denied cases were resubmitted and approved, resulting in an overall approval rate of 92%.

To ascertain the impact of court approval on the medications requested, we examined the final orders of the courts. We found that among the 326 cases in which we could document specific medication orders, 96% (N=313) had no change from the requesting doctor's medication orders; 87% (N=284) were for an antipsychotic (neuroleptic) agent. In about 20% of these requests to use antipsychotic drugs, the agent and dose were not specified. The rank order of the most frequently requested antipsychotics was fluphenazine (26%), haloperidol (20%), chlorpromazine (6%), thiothixene (6%), and thioridazine/mesoridazine (5%). Lithium was the first drug listed in 30 applications, and other psychotropic agents (e.g., lorazepam, antidepressants, and carbamazepine) were the primary agents listed in 10 applications. Laboratory tests were requested in two cases, and six applications involved drugs for medical conditions.

In the cases in which applications were denied (N=28), refusal of medication occurred later in the patients' hospitalization than it did in the approved cases, although the difference was not significant (722±2319 days and 424±1435 days, respectively; t=0.67, df=29, n.s.). In reviewing the time to action, we found that the 22 applications (6%) which required the most time (91–547 days) were more likely to receive decisions denying the physician's request (there was a trend toward significantly greater mean±SD time to action for denied than for approved applications: 70.1±103 versus 35.2±28 days; t=1.78, df=27, p<0.09).

Comparisons of the approved and denied cases on sociodemographic and clinical variables revealed that significantly more women (64%, N=18) than men (36%, N=10) were the subjects of denied applications ($\chi^2$=7.45, df=1, p<0.006), but there were no differences in age, ethnicity, legal status at the time medication was refused, diagnostic group, discharge status at follow-up, or length of hospitalization. Although the absolute number of denied applications was too small for making generalizations, it is worth noting that patients for whom applications were denied had hospital stays of less than 90 days twice as frequently as patients for whom applications were approved.

## DISCUSSION

A discussion of the epidemiology of refusal of psychiatric drug treatment begins with prevalence, but estimation of this statistic depends on how it is operationally defined. When the number of applications for court review is used as the criterion, a 1% rate of refusal of medication is typical. The 1% rate of application to the courts (with a 0.7% rate of court-decided cases) statewide that we found in this study is consistent with earlier findings in court-review programs involving Massachusetts forensic patients (5) and in three single-facility studies in New York (1, 6, 7). The prevalence rises to nearly 2% when it is estimated as a proportion of the involuntary population, the immediate population at risk for refusal of medication. This narrow spectrum of refusers may be the sickest individuals, those most threatening to patient/staff safety, or those for whom applications are most likely to be favorably reviewed (e.g., those with criminal status). Alternatively, the low prevalence may simply reflect the aversion of some physicians to participating in judicial proceedings.

While the prevalence rate of refusal of medication in this survey was virtually identical to the rates reported for other rights-driven programs, it was substantially lower than the rates reported for pioneer in-house clinical review (e.g., 17% in the original Minnesota treatment review panel approach [8]) and the 7% rate in the recent prospective clinical study by Hoge et al. (9), both of which were primarily treatment-driven. Treatment-driven approaches identify a greater proportion of noncompliance with psychotropic regimens, which is generally believed to have a prevalence of as much as 50% in the chronically psychotic population (10). Thus, the front-end court procedure, which is primarily based on a competency determination, has reduced the likelihood of achieving the clinical goal of ensuring appropriate treatment-decision review (e.g., regarding neuroleptic dosage, drug combinations, and longitudinal monitoring) for the majority of potential refusers in the absence of a preceding or parallel treatment-driven adjudication program.

The more frequent use of court adjudication for pharmacotherapy of patients with criminal commitment status suggests the need for more intensive investigation of the use of medication for such patients, since there is little published material on this topic. Such research is particularly critical in view of the recent Supreme Court ruling in *Washington v. Harper* (11). When a criminal patient refuses medication, is the case more likely to be referred to court because he or she is a greater threat to the staff and the other patients? Competing explanations are 1) that patients who refuse medication are generally perceived as a greater risk, as was seen in a comparison of Minnesota refusers and consenters (12), and 2) that the staff may be motivated to apply for court review because of the greater expectation of a favorable outcome when the patient's record indicates crime-associated mental illness.

Regarding the time pattern of court review, time to refusal of medication is a complex process involving the interaction of the individual patient, illness factors, drug treatment, and the therapeutic alliance. Interestingly, while the majority of refusals occurred during the first few months of the patients' current admissions, a substantial minority (more than 25%) occurred later in the hospital course. The reasons for this phenomenon remain speculative at present but are worthy of further study. For example, do these later refusals represent rupture of previously functioning therapeutic alliances, the exacerbation of chronic psychosis, or, conversely, clinical improvement in previously compliant patients who now may have a greater capacity to object to treatment which was previously accepted passively? Passive acceptance of therapy is emphasized by Winick (13) in the current dialogue on patients' capacity to give informed consent or refuse treatment; due process may inadvertently result in the application of higher standards for the patient who refuses medication than for the one who does not. Overall, our findings suggest the need for more intensive clinical examination of the process leading to refusal, in order to identify factors that may be amenable to a treatment-driven adjudication process before the need to initiate a court application. This use of a treatment-driven process before application to the courts might permit the maintenance of a therapeutic alliance (or point out the absence of such) and obviate the need for court adjudication, with its attendant delays and virtually inevitable adversarial intrusion into the subsequent course of treatment.

Time to action is a variable more indicative of the relative efficiency of the clinical and legal administrative processes and includes factors involved in decisions to withdraw applications. In the present study, mean time to action averaged slightly more than 1 month, with no significant difference between applications that were reviewed and those that were withdrawn, suggesting that withdrawal may occur as an 11th-hour decision by the patient, the clinician, or both to seek other means of resolving the treatment impasse. In any event, the 30 days or more during which treatment is presumably at a halt pose a significant cost in terms of treatment resources. In the present study, the delay caused by this waiting period would represent more than 15,000 potentially avoidable hospital days for this group of patients who were the subjects of court review applications in 1 year. Virtually all of the delay is caused by the delay in scheduling and holding a court hearing. The relative inefficiency of this process may be contrasted with treatment-driven clinical review (8), which rarely exceeded 1 week to resolution. In terms of state hospital resources, the addition of 15,000 hospital treatment days in 1 year would result in an annual systemwide cost of more than $3.4 million (personal communication from D. Nonia, Director of Bureau of Costing and Rate Setting, Finance Division, New York State Office of Mental Health, July 1990). To the cost of lengthening the hospitalization of refusers one must add the time and expense of court preparation and appearances for both the clinical team and the legal representatives of the patient and of the hospital.

From the perspective of the patient and the staff, the 30-day delay in initiation of treatment often means considerable unnecessary suffering, with the ongoing potential for physical harm to both patients and staff, as noted by Hoge et al. (9). This is an additional drawback to the rights-driven process and could be seen as a violation in itself of the patient's right to due process. Further study is needed to determine the cause and effect of the outlier situations in which the time to action exceeded the 30-day average, particularly the 16% requiring more than 2 months for action.

The high proportion (28%) of applications withdrawn before court review represents a substantial expenditure of time and paperwork with dubious benefit. Withdrawn applications are an important consideration in developing a model for pharmacological due process. Anecdotal reports of reasons for withdrawal of applications include instances in which patients agreed to take the medication, in which they lacked motivation to persist because they did not expect a satisfactory decision (14), and in which the prescribing doctor felt medication was no longer necessary. In cases of this last kind, the medication may not have been required because the patient left the hospital against medical advice or was discharged. Currently, there is no indication whether there was any clinical resolution following these withdrawals. The earlier discharge of patients whose applications were withdrawn and their greater frequency of discharge without follow-up are consistent with the clinical impression that when an application is withdrawn from the review process, the result is rapid discharge of the patient, which may imply little or no clinical benefit. In addition, these patients may have left a facility without consent (escaped) or been discharged without aftercare arrangements, both of which are indicative of an unresolved clinical episode. It would be most ironic to find that court review is perceived by these patients as an incentive to leave the hospital without consent. Informal interviews with some of the more articulate patients and the almost complete approval of forced medication by the courts in this sample support the notion of a bleak patient perspective on court review.

In reviewing the medication requests, the courts simply agreed with the requested medication orders, and these often involved maximum dose ranges as stated in the product information. Furthermore, court directions lacked explicit specifications for longitudinal monitoring of response or side effects. Typically, an order was approved for the duration of the commitment period. For example, approval was given for 6 months of drug therapy with a high-potency agent such as haloperidol in the widest possible dose range within the limits approved by the Food and Drug Administration (1–100 mg/day). Such requests occurred despite growing research evidence of equivocal benefits and substantial risks at doses at the high end of the range (15). Some court-approved applications included the addition of drugs (e.g., carbamazepine, propranolol) for unspecified indications. These data suggest that court review fails to meet the *Rivers* standard of narrowly tailoring drug therapy to individual patients' clinical needs, with ongoing review of risks and benefits (2). Overall, the use of antipsychotic agents followed the pattern observed in this population before the *Rivers* decision (16).

In summary, the first year's experience with the *Rivers* decision has produced mixed results with respect to the two goals of the system. The legal goal of ensuring a judicial review of competency to refuse treatment appears to have been technically achieved, at least for the 0.7% of the patient population whose cases received a court hearing. However, questions remain regarding the "due process" afforded patients whose cases were withdrawn before a hearing and patients whose refusal of medication failed to reach the court-application stage. Treatment-driven systems tend to provide an avenue for refusal to a much larger proportion of patients, some of whom will have their right to refuse upheld, assuming that external expertise is available for a serious clinical review. When failure occurs in this arena, the patient's right should be further articulated and negotiated, and court review should be undertaken. The court-driven system, including that under *Rivers*, is used relatively rarely and, it seems, almost exclusively for cases in which the legal outcome is clear, namely, where a determination of incompetence to refuse medication is virtually assured. Whereas refusers in the treatment-driven system in Minnesota, described earlier (17), had a one-in-three chance of having their refusal upheld by the internal review process, there was less than a 10% probability of this in the present study. Unfortunately, the treatment-driven approach was undermined in 1988 by the Minnesota Supreme Court decision in *Jarvis v. Levine* (18), which found that the internal review was insufficient to protect the patient's right to refuse treatment; a clinical director had medicated a patient despite the review panel's recommendation to the contrary. This failure points out the need for access to judicial review at some level. The *Jarvis* decision notwithstanding, in-house treatment review is the most viable approach to sorting out the complex of illness, side effects, and dissatisfaction with drug therapy. Furthermore, when the delay of a month or more in obtaining a court hearing is added to the limited outcome from the patient's perspective, a case could be made that patients' rights are more violated than upheld in the rights-driven system, to say nothing of the increased expenditure of treatment and legal resources to implement what appears to be a *pro forma* exercise.

With respect to the clinical goal of the *Rivers* decision, namely, the review and monitoring of the appropriateness of the proposed treatment, the courts in the first year of review appear to have deferred to the treatment team's judgment in the vast majority of cases. From the study data, there appeared to be little use of external court-appointed clinical reviewers and virtually no modification by the courts of the proposed treatments. In addition, the courts did not require subsequent monitoring of treatment for risks and benefits or any follow-up report to the court regarding treatment outcome. The study findings suggest that considerable modification of the *Rivers* process is indicated if the legal and clinical goals of pharmacological due process are to be achieved. A treatment-driven review should be done before the initiation of the rights-driven process, so that patients have the broadest access to an adjudication process which can efficiently and effectively review the technical aspects of appropriate clinical treatment. While an abbreviated form of in-house "second opinion" consultation now usually precedes court application, this process should be revised. Innovative, less expensive in-house treatment programs could be developed by integrating the expertise of psychopharmacology and inpatient psychoeducation specialists so that patients' resistance can be addressed within a psychosocial treatment model (19). This type of program would focus on longitudinal monitoring of the negotiated drug regimen and include patients' reports of medication effects and side effects as an integral part of the treatment evaluation.

The rights-driven court procedure must ensure a timely review of the specific legal question, namely, competence to refuse medication. Finally, the question of court involvement in determining the appropriateness of the proposed treatment regimen should be resolved. On the one hand, treatment decisions are beyond the legal system's expertise. Therefore, it could be argued that such a review of appropriateness is not a legitimate goal for a rights-driven process. On the other hand, the current *pro forma* nature of judicial decisions in this area indicates that the incompetent patient is not receiving review by an impartial expert as required by due process. Clearly, some system for independent review by clinical experts after the hearing needs to be incorporated into the due process system. To avoid further delays, these reviews might be authorized but not operated by the court.

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# Tranylcypromine Versus Imipramine in Anergic Bipolar Depression

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*Objective: This investigation compared the efficacy of the monoamine oxidase inhibitor (MAOI) tranylcypromine with that of the tricyclic imipramine in the treatment of anergic bipolar depressive illness. Method: A controlled, double-blind comparison was used to study 56 outpatients who met operationalized criteria for anergic bipolar depression. Patients with bipolar I and II depression were equally distributed between comparison groups. Outcome was measured by the patient-rated Beck Depression Inventory and the clinician-rated Hamilton Rating Scale for Depression, Raskin Mania and Depression Scales, Clinical Global Impression Scale, and the Pittsburgh Reversed Vegetative Symptom Scale. Twenty-eight patients were treated with tranylcypromine and 28 with imipramine. Seventy-three percent of bipolar depressive patients screened for the study met criteria for anergic depression, consistent with previous findings from studies in bipolar illness that stretch back over 100 years. Results: Tranylcypromine produced statistically significant superior outcome in terms of lower attrition, greater symptomatic improvement, and higher global response without increased risk of treatment-emergent hypomania or mania. Conclusions: The authors propose that the apparently superior efficacy of tranylcypromine in bipolar depression is specifically linked to anergia and reversed neurovegetative symptoms. Bipolar I and bipolar II patients had comparable outcomes, but bipolar I patients had a significantly greater risk of treatment-emergent mood swings. Although the relatively poor showing of imipramine warrants close scrutiny, these findings provide further documentation of the utility of MAOIs in patients presenting with anergia, motor retardation, hyperphagia, and/or hypersomnia.*

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> The mills of God grind slowly,
> but they grind exceeding small.
>
> —Friedrich von Logau

Surprisingly little is known about the acute treatment of the depressed phase of bipolar affective disorder (1, 2). In contemporary clinical practice, the treatment of bipolar depression often follows *pari passu* from the treatment of unipolar illness; i.e., tricyclics such as imipramine usually represent the intervention of first choice, either alone or after the initiation of lithium salts (3).

In contrast, interest in the monoamine oxidase inhibitors (MAOIs) has increased over the past decade, not only regarding their use in refractory (4, 5) or rapid cycling (6) cases of bipolar depression, but also as an effective treatment for atypical depression (7–9). Our group has completed a series of open (4, 10) and controlled (5) investigations of the efficacy of the MAOI tranylcypromine. These studies indicate that tranylcypromine, either alone or in combination with lithium carbonate, is effective in bipolar depression, particularly when the depressive episode is characterized by motor retardation, fatigue, volitional inhibition, and reversed neurovegetative features (i.e., hypersomnia or weight gain) (4, 5, 10), a presentation we have defined as anergic depression (11). The current report describes the results of a controlled comparison of tranylcypromine and a standard tricyclic, imipramine, in the treatment of anergic bipolar depression.

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**TABLE 1. Characteristics of Patients With Anergic Bipolar Depression Who Received Tranylcypromine or Imipramine**

| | Tranylcypromine (N=28) | | | Imipramine (N=28) | | |
|---|---|---|---|---|---|---|
| Variable | N | Mean | SD | N | Mean | SD |
| Gender | | | | | | |
| Male | 12 | | | 10 | | |
| Female | 16 | | | 18 | | |
| Race | | | | | | |
| White | 28 | | | 24 | | |
| Nonwhite | 0 | | | 4 | | |
| Age (years) | | 40.2 | 11.6 | | 37.5 | 10.8 |
| Education (years)[a] | | 15.0 | 2.4 | | 13.5 | 2.7 |
| Age at onset (years) | | 26.9 | 7.7 | | 24.0 | 8.4 |
| Length of current episode (months) | | 6.0 | 3.5 | | 6.8 | 3.7 |
| Diagnosis | | | | | | |
| Bipolar I | 11 | | | 13 | | |
| Bipolar II | 17 | | | 15 | | |
| Pretreatment symptom scores | | | | | | |
| Hamilton depression scale (17-item) | | 22.1 | 4.1 | | 23.2 | 5.0 |
| Beck Depression Inventory | | 29.4 | 9.6 | | 32.4 | 10.3 |
| Raskin Depression Scale | | 11.0 | 1.5 | | 10.9 | 1.4 |
| Reversed Vegetative Symptom Scale | | 9.4 | 3.4 | | 10.1 | 2.7 |
| Medication dose (mg/day) | | | | | | |
| Week 1 | | 23.9 | 5.7 | | 122.0 | 32.0 |
| Week 2 | | 30.7 | 8.3 | | 147.5 | 49.9 |
| Week 3 | | 33.1 | 10.4 | | 186.0 | 44.0 |
| Week 4 | | 36.2 | 12.4 | | 196.5 | 56.0 |
| Week 5 | | 37.7 | 13.0 | | 201.5 | 109.5 |
| Week 6 | | 36.8 | 11.9 | | 245.5 | 69.0 |

[a]Significant difference between groups (t=2.14, df=54, p<0.04).

## METHOD

A total of 56 outpatients in an anergic episode of bipolar affective disorder (defined later) were randomly assigned to double-blind treatment with either tranylcypromine (N=28) or imipramine (N=28) (table 1). All prospective patients completed preliminary psychiatric and medical screening. Patients were excluded from the protocol if they met criteria for another major (axis I) psychiatric disorder, active drug or alcohol abuse, borderline personality disorder, or rapid cycling bipolar disorder (more than four episodes per year). Patients also were excluded if they had a history of intolerance of or nonresponse to either study medication or if they suffered from poorly controlled medical conditions that might either cause depression (e.g., hypothyroidism) or require treatment which contraindicated protocol medication (e.g., asthma). Among over 100 bipolar depressed patients screened for possible intake, 77 were considered eligible at the end of screening.

After screening, potentially eligible patients were carefully evaluated with the following operationalized criteria for an episode of anergic depression: 1) patients must meet the criteria of *DSM-III* and Research Diagnostic Criteria (RDC) (12) for bipolar affective disorder with a current episode of major depression; 2) a minimum score of greater than 15 on the first 17 items of the original Hamilton Rating Scale for Depression (13); 3) the clear-cut presence of fatigue or volitional inhibition; 4) predominant psychomotor retardation as manifested by a score of greater than 2 on item 8 of the Hamilton scale; and 5) the presence of at least one reversed neurovegetative symptom, including either hypersomnia (more than 1 extra hour of sleep each night compared to normal sleep requirement) or weight gain (more than 2.2 kg increase in weight during current episode). These criteria identified 56 of the 77 bipolar patients (73%) otherwise eligible for our study. This frequency of anergic symptoms is consistent with previous investigations (14–17).

We also confirmed the severity of past manic or hypomanic episodes by an independent source (e.g., family member or medical record) to establish the RDC diagnosis of bipolar I or bipolar II subtype. On this basis, 24 patients (43%) met criteria for bipolar I disorder; the remaining 32 patients (57%) met criteria for bipolar II disorder. Review of interrater reliability (by J.M.H. and M.E.T.) revealed a high level of agreement for the presence of an anergic episode of depression (N=77, 92% agreement, kappa=0.83, standard error=0.11, p<0.0001) and for bipolar I versus II subtype (N=56, 89% agreement, kappa=0.71, standard error=0.13, p<0.001).

All patients provided explicit written consent for research participation. The clinical protocol consisted of two phases: a 6-week acute treatment phase, followed by a 10-week period of continuation therapy. Patients were seen weekly by a nurse clinician and psychiatrist during acute treatment and once every 2 weeks during continuation treatment. Only patients who met response criteria continued double-blind treatment past week 6.

Medication capsules were prepared to appear identical and contained inert placebo, 10 mg of tranylcypromine, or 50 mg of imipramine. Patients were provided with two medication containers at each visit, one labeled morning medication (to be taken at 7:00 a.m. and 11:00 a.m.) and the other evening medication (to be taken at 4:00 p.m. and the hour before sleep). Patients treated with tranylcypromine received active medication in the morning and placebo in the evening; the converse was true for patients treated with imipramine. Treatment was initiated at 20 mg/day of tranylcypromine or 100 mg/day of imipramine, and doses were advanced routinely by one active drug unit (i.e., 10 mg of tranylcypromine or 50 mg of imipramine) on the fourth day of the protocol. Thereafter, doses were increased by one active drug unit each week until clinical response occurred, up to the maximum dose of six active drug units/day. Treating clinicians adjusted the dose downward or did not increase it at the maximum rate in cases where significant side effects occurred.

Patients who could not tolerate the side effects of medication at minimum clinically relevant doses (tranylcypromine=30 mg/day, imipramine=150 mg/day) could be withdrawn from the protocol if they were not responding to treatment. Patients were not considered nonresponders unless they completed at least 4 weeks of treatment and reached the minimum therapeutic doses specified earlier. Mean daily doses of tranylcypromine and imipramine are summarized in table 1.

The fidelity of the double-blind procedure was tested by having the treating clinician make a "best guess" of the active agent after week 6 (or end point). Adequacy of treatment was cross-checked in a majority of patients by determination of either the combined blood level of imipramine and desmethylimipramine (N=25; measured by high performance liquid chromatography) or percentage of platelet monoamine oxidase (MAO) inhibition level (N=14) at week 6 or end point. Technical limitations precluded determination of these measurements in the remaining patients.

Depressive symptoms were assessed at each visit with the patient-rated Beck Depression Inventory (18) and the clinician-rated Hamilton scale, Raskin Mania and Depression Scales (19), the Clinical Global Impression Scale (CGI) (20), and Pittsburgh Reversed Vegetative Symptom Scale. The last scale is a 7-item supplement to the Hamilton scale and measures features of an anergic depressive state (21). The Reversed Vegetative Symptom Scale is constructed to correspond exactly with the format of the original Hamilton scale items and to explicitly balance the scale (i.e., relative to items rating melancholic symptoms), with a comparable number of items covering hypersomnia, hyperphagia, and weight gain.

Signs and symptoms of hypomania and mania also were monitored at each visit by the treating clinician. Whenever patients scored greater than 5 on the Raskin Mania Scale, a psychiatrist conducted an independent interview (without knowledge of treatment condition) using RDC criteria. When hypomanic/manic episodes were confirmed, the protocol was terminated, and appropriate treatment of mania/hypomania was begun.

Analyses of acute treatment efficacy were concentrated on results from the first 6 weeks of the protocol. Prescreening of intake data revealed that the two groups differed on only one variable, years of education (table 1). Subsequent analyses indicated that this variable was not significantly related to treatment response or bipolar subtype. Therefore, covariance analyses were not used. Treatment response was defined as a moderate or marked improvement on the CGI (scores of 2 or 3) that was sustained for at least 2 weeks by week 6 or end point. Dichotomous outcome variables (premature attrition, treatment response, and hypomania/mania rates) were compared by using chi-square analysis (corrected for discontinuity), Fisher's exact probability test, or life table statistics. Since we hypothesized that tranylcypromine would be more effective than imipramine, one-tailed tests were performed. The main analyses of the four depression-dependent measures (i.e., Hamilton scale, Reversed Vegetative Symptom Subscale, Raskin Depression Scale, and Beck inventory) were conducted by using a two-factor multivariate analysis of variance (MANOVA) with repeated measures. This analysis yielded main effects for Time (i.e., weeks of treatment), Diagnosis (bipolar I versus bipolar II), and Drug (tranylcypromine versus imipramine), as well as for the interactions of these variables. The MANOVA was first performed with end-point scores, then repeated with data from only those patients who completed the full 6-week protocol. Univariate two-factor analyses of variance (ANOVA) with repeated measures subsequently were computed for each dependent measure when overall effects were significant. Significant main effects and interactions were further explicated by a series of within-subjects (Student-Newman-Keuls tests) and between-subjects (Bonferroni-corrected t tests) comparisons.

**TABLE 2. Treatment Outcome of Patients With Anergic Bipolar Depression Who Received Tranylcypromine or Imipramine**

| Treatment and Outcome | Tranylcypromine (N=28) N | % | Imipramine (N=28) N | % | p[a] |
|---|---|---|---|---|---|
| Acute treatment | | | | | |
| Premature attrition | 2 | 7 | 7 | 25 | 0.03 |
| Outcome[b] | | | | | |
| Response | 21 | 81 | 10 | 48 | 0.02 |
| Hypomania/mania | 3 | 12 | 5 | 24 | n.s. |
| Treatment failure | 2 | 8 | 6 | 29 | 0.06 |
| Continuation treatment[c] | | | | | |
| Withdrew | 2 | 10 | 5 | 50 | 0.02 |
| Relapsed | 1 | 5 | 1 | 10 | n.s. |
| Hypomania/mania | 3 | 14 | 2 | 20 | n.s. |
| Sustained remission | 15 | 71 | 2 | 20 | 0.01 |

[a] Fisher's exact probability test except for acute treatment response, where chi-square analysis was used ($\chi^2$=4.3, df=1).

[b] Patient N=26 and N=21.

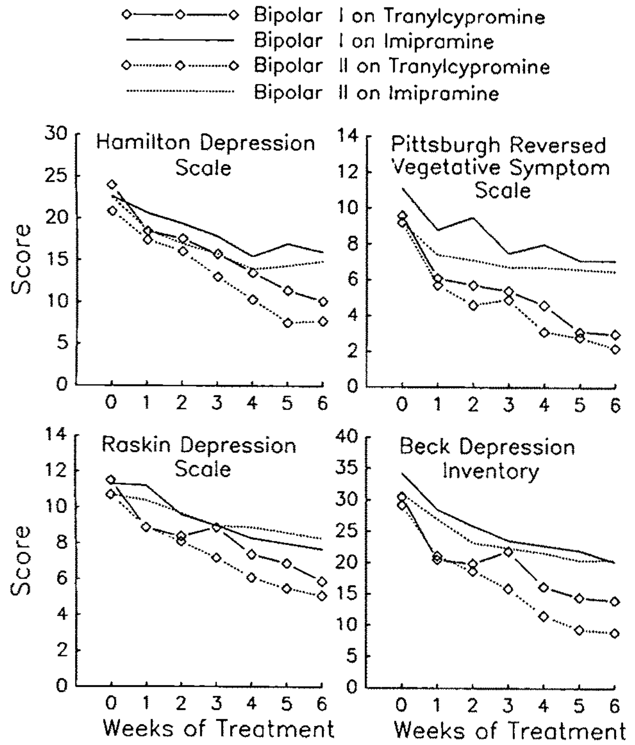
[c] Patient N=21 and N=10.

## RESULTS

Significantly more imipramine patients than tranylcypromine patients were withdrawn prematurely from the protocol (N=7 [25%] versus N=2 [7%]; p=0.03, Fisher's exact test). Among the patients who completed 4 or more weeks of treatment (tranylcypromine, N=26; imipramine, N=21), a significantly greater number of patients in the tranylcypromine group responded to acute treatment (N=21 [81%] versus N=10 [48%]; p=0.02; table 2). A similarly significant advantage was found for tranylcypromine compared to imipramine by using life table analysis (Wilcoxon $\chi^2$=7.9, df=1, p=0.005).

Mean end-point scores for patients across 6 weeks of the protocol are illustrated in figure 1. Bipolar I and bipolar II patients did not differ on the MANOVA with respect to symptomatic response (figure 1 and

**FIGURE 1. Symptom Rating Scores for Bipolar I and Bipolar II Depressed Patients Treated With Tranylcypromine or Imipramine[a]**



[a] Patients treated with tranylcypromine had significant reductions in symptom scores after week 4 on all four measures (p≤0.01, Bonferroni-corrected t tests).

table 3), nor did bipolar diagnostic subtype interact significantly with Time or Drug effects (table 3). Although patients in both drug groups experienced significant reductions in symptoms (Time effect: F=4.9, df=24, 29, p<0.001), a significant Drug by Time interaction was observed (F=2.4, df=24, 29, p<0.02). Subsequent univariate ANOVAs also yielded significant Drug by Time interaction effects on the Hamilton scale (p=0.03), Reversed Vegetative Symptom Subscale (p=0.03), and Raskin Depression Scale (p=0.02); the interaction term on the Beck inventory just missed significance (p=0.06) (table 3). Analyses partitioning across weeks of treatment and drug group demonstrated that the significant interactions were explained by the more pronounced reduction in symptom scores after week 4 in the tranylcypromine group compared to the imipramine group (figure 1).

Results of the analysis involving only the patients who completed the study were somewhat at variance with those just reported. Significant main effects were again found for Time (F=11.6, df=24, 9, p=0.0003, MANOVA) and Drug (F=3.9, df=4, 29, p=0.01). However, the Drug by Time interaction was not significant (F=1.3, df=24, 9, p=0.36). It was unclear whether this disparity was due to inadequate statistical power in the analysis of only the patients who completed the study (i.e., due to the loss of 20 degrees of freedom) or whether it was an artifact introduced by end-point analysis (i.e., greater attrition in the imipramine group resulted in a large number of unimproved patients' scores being carried on). An additional post hoc analysis was conducted to try to explicate these findings. A series of regression analyses were performed to determine the slope (or rate of symptom reduction) for each patient on each of the four depression measures; these analyses used all data up to the point of attrition or completion of week 6. The resultant values, expressed as beta scores, were then included in a one-factor MANOVA, and a significant effect favoring tranylcypromine was found (F=2.7, df=4, 48, p=0.04). This indicated that the rate of symptomatic improvement was greater in patients treated with tranylcypromine even when the possible bias due to attrition from the imipramine group was minimized.

Median level of platelet MAO inhibition was 83.1% at the end of acute treatment (N=14; range: 30.7%–97.9%). Seven patients (50%) reached a targeted MAO inhibition of 80% or more; treatment response in this group was 71% (N=5 of seven patients); i.e., it was identical to that in patients with lower platelet MAO inhibition levels (N=5 of seven patients). Mean±SD level of combined imipramine and desmethylimipramine was 327.6±223 ng/ml (N=25) (range=56–979 ng/ml); 72% (N=18) of the patients had combined blood levels of a targeted level of 225 ng/ml or more. The response rate of these "adequately treated" patients was 44% (N=8 of 18). Blood levels of imipramine (t=0.76, df=23), desmethylimipramine (t=−0.98, df=23), and the combined values (t=0.39, df=23) did not differ significantly between responders and nonresponders.

Response was sustained across the 10 weeks of continuation treatment in 15 (71%) of the tranylcypromine responders; one patient experienced a depressive relapse and three developed hypomania, which necessitated discontinuation of the double-blind procedure. The mean±SD Hamilton scale score at the end of continuation therapy with tranylcypromine was 4.4±4.5. Only two patients in the imipramine group finished the continuation phase in remission (table 2; p=0.01); the remaining patients either withdrew from treatment (N=5) or were withdrawn because of treatment-emergent hypomania (N=1) or mania (N=1) or depressive relapse (N=1).

A total of six tranylcypromine patients (21%) became hypomanic or manic, as did seven imipramine patients (25%). Onset of treatment-emergent hypomania/mania tended to occur more quickly in patients treated with imipramine than with tranylcypromine (mean onset=5.8±6.1 versus 9.2±4.4 weeks; Mann-Whitney U=7.5, p=0.09). Five of the imipramine-treated patients switched into mania without meeting criteria for antidepressant response. These patients were judged by the treatment team to have mixed (dysphoric-irritable) manic episodes; three patients required hospitalization. On the other hand, five of the

**TABLE 3. Multivariate and Univariate Analyses of Variance of Measures for Patients With Anergic Bipolar Depression Who Received Tranylcypromine (N=28) or Imipramine (N=28)**

| | Main Effects (F) | | | Interaction Effects (F) | | | |
|---|---|---|---|---|---|---|---|
| Analysis | Time[a] | Diagnosis[b] | Drug[b] | Time by Diagnosis[a] | Time by Drug[a,c] | Drug by Diagnosis[b] | Time by Drug by Diagnosis[a] |
| MANOVA | 4.9[d] | 1.4 | 3.2[e] | 0.7 | 2.4[e] | 1.5 | 0.6 |
| ANOVA | | | | | | | |
| Hamilton depression scale | 16.1[d] | 2.1 | 4.1[f] | 0.6 | 2.6[f] | 0.1 | 0.4 |
| Reversed Vegetative Symptom Scale | 15.1[d] | 1.7 | 13.3[d] | 0.6 | 2.6[f] | 0.1 | 0.2 |
| Raskin Depression Scale | 16.5[d] | 0.6 | 7.7[e] | 0.5 | 2.7[f] | 0.7 | 0.6 |
| Beck Depression Inventory | 18.1[d] | 0.8 | 5.9[f] | 0.5 | 2.2 | 0.1 | 0.5 |

[a] df: MANOVA=24, 29; ANOVA=6, 47.

[b] df: MANOVA=4, 49; ANOVA=1, 52.

[c] Time by Drug interactions remained significant when Greenhouse-Geiser adjusted degrees of freedom were used.

[d] p<0.001.

[e] p<0.01.

[f] p<0.05.

six mood swings during tranylcypromine treatment occurred after response to treatment. These patients developed euphoric hypomania; none required hospitalization. The rate of hypomanic/manic episodes was 38% (N=9 of 24) in bipolar I patients across both drug conditions, compared to 13% (N=4 of 32) in bipolar II patients ($\chi^2$=3.7, df=1, p=0.03, one-tailed).

The treating clinician correctly guessed the study drug in 68% (N=38 of 56) of the cases, i.e., a frequency that almost reached statistical significance when compared to a "chance" expectation of 50% ($\chi^2$=3.3, df=1, p=0.07, two-tailed). The proportion of correct guesses did not significantly differ between drugs (tranylcypromine: N=18 of 28; imipramine: N=20 of 28). In most cases, either the presence or absence of characteristic side effects (e.g., anticholinergic or sedative effects for imipramine and insomnia for tranylcypromine) was identified as the basis for the correct guess.

## DISCUSSION

We found that tranylcypromine was significantly more effective than imipramine on both categorical and symptomatic indices of response in anergic episodes of bipolar depression. Such efficacy was generally sustained and was not associated with an increased risk of treatment-emergent mood swings. These findings complement and extend our earlier work with patients with depression resistant to tricyclics (4) and in mixed samples of patients with anergic depression (5, 10). Liebowitz, Quitkin, Klein, et al. (8, 22, 23) have similarly found that phenelzine is more effective than imipramine in patients with nonbipolar depression characterized by sensitivity to rejection, fatigue, hypersomnia, or hyperphagia. While the patients of Liebowitz et al. were less severely ill and more mood-reactive than those in our bipolar sample, our group also has recently replicated the utility of MAOIs in a more severely depressed sample of patients with tricyclic-resistant, anergic unipolar depression, including patients with reactive and nonreactive mood disturbances (21). We thus believe that the apparent efficacy of tranylcypromine in the present group of patients with bipolar depression is specifically linked to the presence of anergia and reversed neurovegetative symptoms.

Our study also provides new data concerning treatment-emergent hypomanic and manic episodes. This topic remains quite controversial (1). However, the observation of a 38% risk of hypomania/mania in bipolar I patients over a period of 16 weeks or less suggests a process "driven" by antidepressant treatment. Our observations regarding the speed of onset and severity of imipramine-related mood swings should be considered preliminary but could provide an important clue for future studies, particularly because a number of the imipramine patients who switched did so without passing through a normal mood phase.

The relatively poor response to imipramine observed in the current study requires careful scrutiny. At one level, patients suffering from anergic depression may be relatively intolerant of the side effects of standard tricyclic antidepressants. In our current protocol, a large number of imipramine nonresponders were unable to tolerate doses greater than 200 mg/day. It is conceivable that a longer period of treatment at smaller doses (i.e., 100–150 mg/day) might have improved the imipramine response rate. We have suggested elsewhere (11) that the sleep profile of anergic depression (increased REM sleep indices, preservation of slow wave sleep, and normal sleep maintenance) may point to an underlying neurobiological substrate for preferential response to MAOIs. In contrast, poor response to imipramine may be linked to its inherent pharmacological properties, especially atropinism and sedation. If this is true, then use of a heterocyclic with less sedative effects, such as desipramine, or a second-generation agent, such as fluoxetine, might have yielded better results.

Alternatively, the absence of concurrent treatment with lithium salts in this protocol may also be related to the comparatively poor showing of imipramine. Lithium has been found to augment the efficacy of tricyclic antidepressants (24). However, our investigation suggests that imipramine alone is as poor a treatment of anergic bipolar depression as tranylcypromine alone is a strong treatment. A possible explanation of this conundrum is that the treatment of bipolar depression requires a strong perturbation of serotonergic mechanisms and that tranylcypromine's effectiveness may be linked to more potent direct effects on such mechanisms (25). Imipramine, on the other hand, may require the presence of lithium in anergic depression to similarly affect serotonin metabolism (26). A majority of practitioners prescribe lithium salts concurrently with tricyclic antidepressants in the treatment of bipolar depression (1–3), and this practice may enhance the apparent efficacy of the tricyclic antidepressant.

Questions about the validity of our definition of anergic depression, our enrollment of bipolar II patients, the adequacy of tricyclic treatment, and our protection of the double-blind procedure also deserve comment. First, the operationalized criteria developed to define anergic depression have not yet been used outside of Pittsburgh. While there is no consensus as to whether anergic depression is a common or uncommon presentation, there is abundant documentation that fatigue, motor retardation, and reversed neurovegetative features are associated with bipolar depression (14–17). We hope that these findings will stimulate other researchers to investigate the validity of the anergic depression construct.

Second, at the beginning of this study we did not consider the inclusion of bipolar II patients to be a limitation. However, more recent data (17, 27, 28) indicate that bipolar I patients and bipolar II patients may differ with respect to family history and clinical course. These findings are further supported by our own observation of a higher rate of treatment-emergent mood swings in bipolar I patients. Although we did not find any relationship between bipolar subtype and symptomatic response to tranylcypromine, in future studies we plan to focus specifically on bipolar I depression.

Third, with respect to treatment adequacy, treatment response to imipramine or tranylcypromine appeared to be unrelated to tricyclic plasma level or percentage of platelet MAO inhibition, respectively. It is of interest that the drug with the higher response rate (tranylcypromine) had the larger number of patients below the arbitrary pharmacological standard. It is conceivable that there is a therapeutic window for imipramine plus desmethylimipramine in anergic depression and that a number of our tricyclic antidepressant nonresponders were either above or below this window. However, it should be noted that, to our knowledge, there is no published evidence specifically linking tranylcypromine or imipramine response in bipolar depression to these measures. Moreover, tranylcypromine is a mixed MAOI, with prominent type A (tyramine) site inhibition, while platelets contain solely the MAO B form of this enzyme (29). Indeed, as we have reported elsewhere (30), tranylcypromine blood levels seemed distinctly more predictive of both side effects and outcome than did the percentage of platelet MAO inhibition.

Fourth, it appeared that the fidelity of the double-blind procedure was somewhat compromised in our study. The difference in the clinical pharmacology between tricyclic antidepressants and MAOIs may be so dramatic that a skilled pharmacotherapist cannot remain truly blind in a majority of cases; this conclusion is also suggested by the findings of Rabkin et al. (31). Nevertheless, this raises the possibility that experimenter bias influenced results. In future studies, it may be necessary to use additional measures to protect the blind procedure, such as use of independent evaluators who assess response but not side effects or who rate response through use of edited videotapes.

In summary, although the factors that we have discussed require consideration, our findings strongly suggest that tranylcypromine is more effective than imipramine in the treatment of anergic episodes of the depressed phase of bipolar illness. The efficacy of tranylcypromine in agitated bipolar depressive states, of course, remains untested, as does its utility in comparison to (and in combination with) lithium carbonate.

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# 50-Year Trends in the Incidence of Anorexia Nervosa in Rochester, Minn.: A Population-Based Study

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*Objective: The aim of the study was to determine incidence and prevalence rates and long-term trends in incidence of anorexia nervosa by identifying all persons residing in the community of Rochester, Minn., during the 50-year period 1935 through 1984 who had the disorder. Method: From a community-based epidemiologic resource, 13,559 medical records with diagnoses of amenorrhea, starvation, weight loss, anorexia nervosa, or other conditions were screened to identify true cases of anorexia nervosa determined by using standard diagnostic criteria. Results: One hundred eighty-one residents (166 female and 15 male) fulfilled the diagnostic criteria for anorexia nervosa; these were the incidence cases. Due to a quadratic trend in the rates for girls 10–19 years old, the incidence rate among female residents fell from 16.6 per 100,000 person-years in the 1935–1939 period to a low of 7.0 in 1950–1954 and increased to 26.3 in 1980–1984. The incidence rates for women 20 years old and older and for males remained constant. For females 15–24 years old, there was a linear increase. The overall age-adjusted incidence rate per 100,000 person-years was 14.6 for females and 1.8 for males. The prevalence rate per 100,000 population was 269.9 for females and 22.5 for males. Conclusions: Anorexia nervosa is more common than previously recognized. Among girls 15–19 years old it is a very common chronic illness. Its incidence has increased among females 15–24 years old but not among older women or among males.*

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Anorexia nervosa has become an important health problem in Western countries (1). It is associated with severe long-term morbidity and substantial mortality (2–5). Debate has focused on whether the incidence of anorexia nervosa is increasing (6–9). Incidence represents the number of new cases appearing during a time interval, usually expressed as the number of cases per 100,000 person-years (same as cases per year per 100,000 population). Prevalence represents the total number of cases of the disease in a group at a certain time expressed as the rate per 100,000 population or as a percentage. Most estimates have suggested an increase in the incidence of anorexia nervosa since 1950 (10–17) and perhaps since 1930 (18). Although most clinicians interpreted greater numbers of patients with anorexia nervosa seen in practice as signifying a remarkable increase in the occurrence of the disorder, Williams and King (7) in England and Nielsen (19) in Denmark concluded that the apparent rise in anorexia nervosa was not real but was related to changes in demographics and in medical practice. Our population-based study of the incidence of anorexia nervosa in Rochester, Minn., during the 45-year period 1935–1979 (8) failed to reveal a significant trend and identified surprisingly high rates during the 15-year interval between 1935 and 1949. A trend toward an increase in the rates for girls 10–19 years old, albeit not statistically significant, was noted for the period 1950–1979. A considerable increase in incidence in females with the illness during the final 2 years of the study was a compelling reason to extend the study for another 5 years to determine whether that trend would continue.

Rochester is a Midwestern city located about 75 miles southeast of Minneapolis. It is the county seat of Olmsted County, a grain and dairy farming region. Its population was approximately 60,000 in 1985 and

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**TABLE 1. Diagnostic Categories Reviewed to Identify All Cases of Anorexia Nervosa in Rochester, Minn., 1935–1984**[a]

| Diagnostic Category | Number of Records Screened | Cases of Anorexia Nervosa Identified N | % |
|---|---|---|---|
| Anorexia nervosa | 231 | 97 | 42.0 |
| Anorexia | 826 | 15 | 1.8 |
| Amenorrhea | 3,789 | 70 | 1.8 |
| Oligomenorrhea | 878 | 14 | 1.6 |
| Anovulation, irregular menstruation, menstrual dysfunction | 2,120 | 5 | 0.2 |
| Ovarian dysfunction, hypo-ovarianism | 607 | 3 | 0.5 |
| Delayed puberty, delayed menarche | 428 | 1 | 0.2 |
| Delayed menstruation | 181 | 2 | 1.1 |
| Starvation, weight loss, underweight, malnutrition | 1,483 | 51 | 3.4 |
| Inadequate diet | 1,775 | 4 | 0.2 |
| Nutritional disturbance, marasmus | 377 | 0 | 0.0 |
| Anasarca, edema, hydrops | 138 | 0 | 0.0 |
| Addison's disease | 54 | 0 | 0.0 |
| Simmonds' disease | 52 | 1 | 1.9 |
| Malaise | 61 | 0 | 0.0 |
| Nervous exhaustion | 344 | 1 | 0.3 |
| Nervous stomach, psychogenic gastrointestinal disorder | 12 | 0 | 0.0 |
| Vomiting | 203 | 0 | 0.0 |
| Total | 13,559 | 264[b] | 1.9 |

[a] Data are from Mayo Clinic records and other sources.

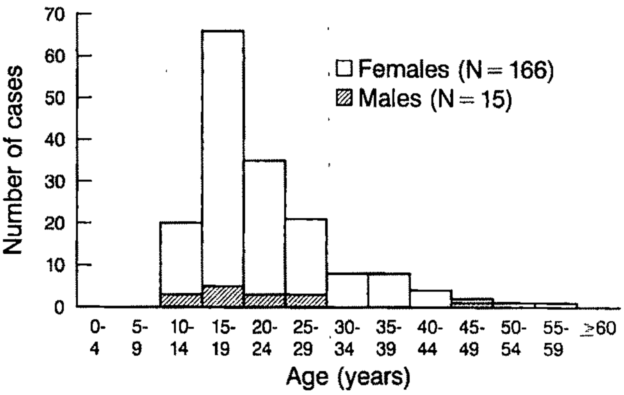
[b] 213 incidence and prevalence cases were identified; some appeared in more than one diagnostic category.

23,000 in 1935. Although the local economy once was based chiefly on farming and light industry, the Mayo Medical Center and IBM are now the largest employers in the city. The homogeneous population is primarily of northern European origin. In 1980, the racial composition was 98% white. Compared with the U.S. population, there was a relatively greater proportion of female residents between the ages of 15 and 25 years.

## METHOD

The medical records in the Mayo Clinic epidemiologic archives and in the files of other health-care providers in the surrounding geographic area were examined for residents of Rochester, Minn. We screened for approximately 30 diagnostic terms and particularly for amenorrhea, oligomenorrhea, starvation and weight loss from any cause, and anorexia nervosa (table 1). For patients with these diagnoses the original medical records were reviewed and the diagnosis of anorexia nervosa determined or confirmed by using *DSM-III-R* and the criteria of the Pathology of Eating Group (20). Thus, we were able to identify a large number of patients not previously diagnosed as having anorexia nervosa. Those who were so diagnosed previously but did not meet the criteria were excluded. Most of these patients had never been hospitalized for their illness, and many had not seen a psychiatrist.

**FIGURE 1. Distribution of Age at Diagnosis of Anorexia Nervosa Among Female and Male Residents of Rochester, Minn.**



Records with diagnostic coding for depressive illnesses were not screened separately, although many of the anorexia nervosa patients had depressive symptoms and some developed major depression after the onset of anorexia nervosa. The depressed patients who had notable weight loss or menstrual dysfunction appeared on those diagnostic lists and thus were identified as potential anorexia nervosa cases.

Diagnostic certainty was rated as definite, probable, and possible on the basis of the completeness of the information available in the records. When incidence data were analyzed separately for these groups, for the first 45 years of the study the trends did not differ appreciably from the overall trend for all subjects combined (8). Therefore, we combined the groups to analyze data for the entire 50-year span of the study.

Criteria were applied consistently throughout the duration of the study, maximizing the likelihood that a comparable group of subjects was identified over time.

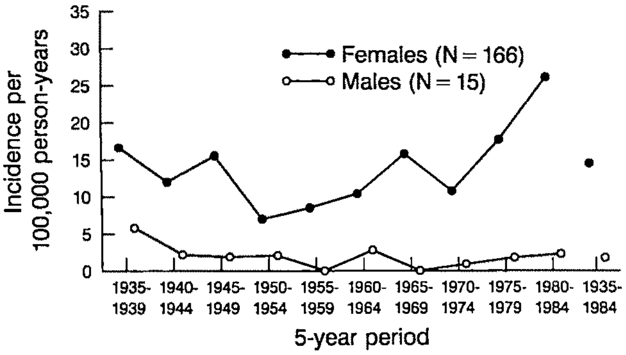
The background of the study and the Mayo Clinic epidemiologic archives have been described previously (8, 21, 22).

Tests of trends in incidence rates were performed by using generalized linear models (23) with Poisson error structure. Tests for linearity of trend have one degree of freedom, and quadratic models have two degrees of freedom.

## RESULTS

During the 50-year period 1935–1984, 166 females and 15 males who had been residing in Rochester for at least 1 year developed anorexia nervosa. The mean ± SD age at diagnosis of the females was 21.7±8.3 years (median=19 years, range=10–57 years); for the males it was 20.9±9.0 years (median=18 years, range=12–49 years). The age distribution is shown in figure 1. Age-adjusted (to the 1970 U.S. white population) incidence rates by 5-year periods are shown in figure 2.

FIGURE 2. Age-Adjusted[a] Incidence Rates for Anorexia Nervosa in Female and Male Residents of Rochester, Minn., by 5-Year Periods



[a] Adjusted to 1970 U.S. white population.

TABLE 2. Age- and Sex-Specific Incidence Rates for Anorexia Nervosa Among Residents of Rochester, Minn., 1935–1984[a]

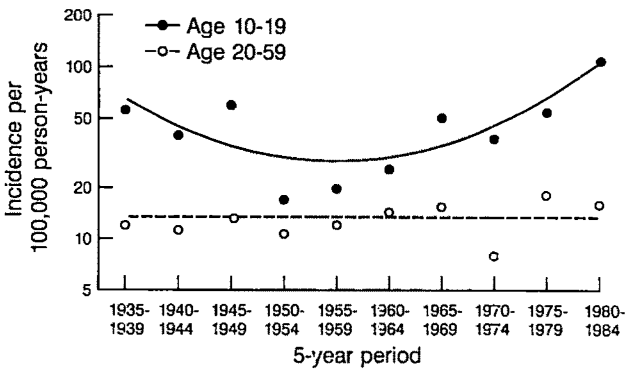
| Age Group (years) | Incidence per 100,000 Person-Years | | |
|---|---|---|---|
| | Females | Males | Total |
| 0–9 | 0.0 | 0.0 | 0.0 |
| 10–14 | 25.7 | 3.7 | 14.6 |
| 15–19 | 69.4 | 7.3 | 43.5 |
| 20–24 | 27.6 | 4.6 | 19.9 |
| 25–29 | 20.7 | 3.6 | 13.0 |
| 30–39 | 10.9 | 0.0 | 5.6 |
| 40–49 | 5.2 | 1.0 | 3.2 |
| 50–59 | 2.0 | 0.0 | 1.1 |
| 60 and older | 0.0 | 0.0 | 0.0 |
| Total | 15.1 | 1.7 | 9.0 |

[a] Age-adjusted (to 1970 U.S. white population) rates: females, 14.6; males, 1.8. Age- and sex-adjusted rate: 8.2.

The overall age-adjusted incidence rate for females was 14.6 per 100,000 person-years; for males it was 1.8 per 100,000 person-years. Thus, anorexia nervosa was found 8.1 times more frequently in females than in males. The overall age- and sex-adjusted rate was 8.2 per 100,000 person-years. Age- and sex-specific incidence rates are shown in table 2. The incidence rates for females 10–19 years old and 20–59 years old are shown in figure 3.

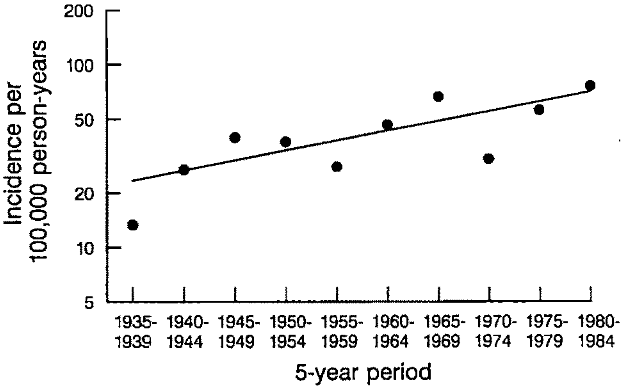
The age-adjusted incidence rates of anorexia nervosa in females residing in Rochester have increased from a low of 7.0 per 100,000 person-years in 1950–1954 to a high of 26.3 in 1980–1984. This increase is due primarily to the highly significant linear trend in the incidence rates for females 10–19 years old ($p < 0.001$). The estimated coefficient indicates that, on the average, the incidence rates increased by 36% every 5 years over the 35 years from 1950 to 1984. When the entire scope of the study is considered (1935–1984), the incidence rates for females 10–19 years old show a highly significant quadratic trend ($p<0.001$). In contrast, incidence rates in females 20–59 years old were stable throughout the 50-year period.

FIGURE 3. Age-Specific Incidence Rates[a] for Anorexia Nervosa, by 5-Year Periods, in Two Age Groups of Female Residents of Rochester, Minn.[b]



[a] Plotted on a log scale.
[b] Observed=circles, predicted=lines.

FIGURE 4. Age-Specific Incidence Rates[a] for Anorexia Nervosa, by 5-Year Periods, in 15–24-Year-Old Female Residents of Rochester, Minn.[b]



[a] Plotted on a log scale.
[b] Observed=circles, predicted=line.

The age-adjusted incidence rates of anorexia nervosa in females 15–24 years old, the most vulnerable group, showed a highly significant linear increasing trend from 1935 to 1984 ($p<0.001$) (figure 4). This age group represented 101 (60.8%) of the female cases.

On Jan. 1, 1985, 99 females and six males with a history of anorexia nervosa were alive and residing in Rochester. The crude prevalence rate per 100,000 persons based on these cases was 306.0 for females and 22.2 for males (the female population in Rochester was 32,353, and the male population was 27,067). The age-adjusted (to the 1970 U.S. white population) prevalence rates were 269.9 (95% confidence interval=213.6–326.2) for females and 22.5 (95% confidence interval=3.9–41.2) for males. Thus, the illness was 12.0 times more frequent in females on the prevalence date. The overall sex- and age-adjusted prevalence rate was 149.5 (95% confidence interval=119.3–179.7).

Among girls 15–19 years old, the prevalence rate was 480.3 per 100,000 persons.

## DISCUSSION

Anorexia nervosa is often considered an illness primarily of adolescent girls. Yet it was identified in persons of both sexes and at onset ages ranging from 10 to 57 years. There was much diversity among the patients in regard to magnitude of weight loss and psychological manifestations despite their common characteristics of self-imposed weight loss of at least 15%, amenorrhea in females, and a psychological disorder relating to eating. Thus, the study group represented the spectrum of the disease occurring in the community. In contrast, referred psychiatric subjects and hospitalized patients constitute a selected group with illness of greater severity.

Analysis of incidence data from all females for the 45 years through 1979 did not reveal a significant trend. However, there were indications that subjects within different age groups had different trends over time. These age-specific differences became more apparent when incidence data for 50 years were analyzed.

In the 5-year period 1980–1984 the incidence rate of anorexia nervosa in Rochester among girls 10–19 years old (109.8 per 100,000 person-years) and particularly among those 15–19 years old (155.9 per 100,000 person-years) had increased to a remarkably high level. The rates for older women remained relatively constant. Among males the disorder remained rare with no appreciable change in the rates over time. During 1980–1984 anorexia nervosa occurred 11.6 times more frequently in females than in males.

The high rate among girls 10–19 years old, and particularly among those 15–19 years old, makes it the third most common chronic illness among adolescent girls after obesity and asthma. The prevalence of obesity is subject to debate because of differences in standards for determining the degree of overweight that is pathological. Depending on the criteria for obesity, estimates of its prevalence vary between 10% and 25% of the adolescent population (24, 25). The prevalence of asthma among schoolchildren and young adults is between 5% and 10% (26, 27). Anorexia nervosa occurs in 0.48% of the 15–19-year-old girls in Rochester. In comparison, insulin-dependent diabetes mellitus occurs in 0.1% of school-age children (28).

Although a significant trend in incidence was not observed during the 30-year period 1950–1979, data for the subsequent 5 years indicated a sharp increase. This trend (but not the rates) is in agreement with the observations of other investigators in Sweden (18), Denmark (11), Great Britain (10, 12, 13, 17), Switzerland (15), The Netherlands (16), and the United States (13, 14). Psychiatric case register studies found rates per 100,000 population as high as 5.0 (16), and a Dutch study seeking cases through general practitioners found an incidence of 6.3 per 100,000 during 1985 and 1986 (unpublished 1988 paper by H.W. Hoek). An incidence study in a Swedish suburban area seeking cases through medical and nonmedical caregivers during 1984 and 1985 (29) yielded an annual incidence of 2.6 per 100,000 (43 per 100,000 for females 16–24 years old); the prevalence was 22 per 100,000 (258 per 100,000 for females 16–24 years old). In South Australia (30), only six cases of anorexia nervosa were identified among 5,705 girls in secondary school, representing a prevalence of 105 per 100,000. Willi et al. (31, 32) extended their study of hospitalized patients in Zurich. They found an increase in anorexia nervosa among females with onset between ages 12 and 25 years from 1956 to 1973 but not from 1973 to 1985. Our rates for each era in Rochester are considerably higher than those reported in these previous studies, probably because of more complete case ascertainment.

In a survey of an entire school population of 15-year-olds in Göteborg, Sweden, in 1985, Råstam et al. (33) found a prevalence rate of 0.84% for girls and 0.09% for boys. This rate for girls is even higher than the prevalence rate of 0.48% that we found for girls 15–19 years old. However, a countywide survey of nonreferred students 14–17 years old in New Jersey (34), which used the older, stricter *DSM-III* criteria for anorexia nervosa, reported a prevalence rate of 0.3% for girls.

Theander (18) observed an incidence of only 0.08 per 100,000 in a region of Sweden in the period 1931–1940. However, that rate was based on patients with severe anorexia nervosa hospitalized for their illness. The severity of disease tends to be greater in clinical referral-based studies than in population-based studies. Moreover, diagnostic criteria became less stringent over time. Although *DSM-III-R* criteria were not published until 1987, we applied those standards to evaluate all records regardless of the year the illness began. Thus, we used consistent diagnostic criteria throughout the 50-year period even though standards for diagnosing anorexia nervosa were changing (35). This may be part of the reason why our rates for 1935–1949 are so much higher than Theander's. It is also possible that there are national and regional differences in the frequency of anorexia nervosa, but we suspect that such differences are not great in Western countries.

Case records of all persons living in Rochester, Minn., who had ever visited a physician came under scrutiny in our study. Although a few individuals with anorexia nervosa undoubtedly were missed because they never visited a physician or because their medical records made no mention of weight or weight loss, these false-negative cases should be relatively rare. Almost all residents of the community had visited a health-care provider during the period of study. It would be rare for an individual with substantial weight loss not to have come to medical attention. When diagnostic criteria for anorexia nervosa were met, we included subjects seen by nonpsychiatric physicians who assigned diagnoses such as amenorrhea and underweight. This resulted in more complete case ascertainment than in previous studies.

The inclusion of false-positive cases was highly unlikely because the original medical records were carefully scrutinized. Even the earliest records typically contained thoroughly detailed histories and reports of physical findings handwritten by physicians. In some instances, information about psychological attitudes toward food and eating was incomplete or lacking, and the fear of gaining weight could not be confirmed. However, when there was an inordinate weight loss unaccounted for by other physical disease, anorexia nervosa was the most likely cause. We believe that our incidence rates represent minimum estimates of the true rate in the Rochester population. The prevalence rate on Jan. 1, 1985, may be an underestimate because some individuals who had anorexia nervosa earlier in life and who recovered before they moved to Rochester might not have been identified.

The clinical diversity among the affected persons in this population-based study was striking. In contrast to referral-based studies that report a high percentage of patients with poor outcome despite treatment (36), it was not unusual for affected persons in our study to recover with little or no formal treatment. This was ascertained by anecdotal information in the medical records. Conclusions about long-term outcome, however, must await the completion of a case-control study.

Will the increase continue? It would be injudicious to predict future trends, but we doubt that the recent increase will continue, at least not at the same rate. Clinical experience suggests that anorexia nervosa reached a peak in the early 1980s. In its place, the rate of bulimia nervosa and milder forms of the binge-purge syndrome has increased substantially among women who maintain weight within a relatively normal range (6). We suggest the possibility that there is a cyclic trend in the incidence rate of anorexia nervosa in keeping with changing fashion and idealized body image. The ratios of bust-to-waist and hip-to-waist measurements of women depicted in *Vogue* and *Ladies Home Journal* were low in the 1920s and 1930s, high in the 1950s, and low again in the 1960s and 1970s. Thus, these ratios varied over time inversely with the occurrence of anorexia nervosa in 10–19-year-old girls. The thin, noncurvaceous standard preceded the time periods when the rates for anorexia nervosa were highest (37). However, social and psychological pressure to be thin to the extent that weight loss becomes severe enough to result in anorexia nervosa affects only a very small proportion of the general population. If most young women were overwhelmed by the cultural obsession with thinness, then anorexia nervosa would be much more common than it is. Most individuals probably have a physiological protective mechanism that prevents them from losing weight excessively, even after stringent efforts to diet.

We suspect that the most severe form of the illness requires a biological predisposition that has not yet been elucidated (38). We also suspect that this severe form of anorexia nervosa has occurred at a relatively constant rate over time. A milder form among teenage girls, the ones who are most vulnerable to social pressure, may explain the varying rates.

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# The Relation Between Hypochondriasis and Age

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Objective: *This study examined the relation between hypochondriasis and age while controlling for the possible confounding influences of medical morbidity, social isolation, and other psychiatric disorder.* Method: *Consecutive patients attending a general medical clinic on randomly selected days were screened with a hypochondriasis self-report questionnaire. Those whose scores exceeded a preestablished cutoff level and a random sample of those who scored below it completed a research battery consisting of self-report questionnaires and structured interviews for* DSM-III-R *diagnoses of hypochondriasis and other axis I disorders. The patients' medical records were audited, and their physicians completed questionnaires about them. The 60 patients who met the* DSM-III-R *criteria for hypochondriasis at interview constituted the study group, and 100 patients randomly chosen from among those who scored below the cutoff for hypochondriasis constituted the comparison group.* Results: *The hypochondriacal group was not older than the comparison group. Hypochondriacal patients aged 65 years and over did not differ significantly from younger hypochondriacal patients in hypochondriacal attitudes, somatization, tendency to amplify bodily sensation, or global assessment of their overall health, even though their aggregate medical morbidity was greater. The elderly hypochondriacal patients had higher levels of disability, but this appeared to be attributable to their medical status rather than to any increase in hypochondriasis. Within the comparison sample, subjects aged 65 years and over were not more hypochondriacal than those under 65 years of age.* Conclusions: *Hypochondriasis is found to some degree in all patients and appears to be unrelated to age.*

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The relation between hypochondriasis and aging is unclear. Some research suggests that the elderly are more hypochondriacal, more prone to preoccupation with their bodies, and more likely than younger people to describe their physical health as poorer than it is (1–5). Other studies contradict the stereotype of elderly persons as preoccupied with their health and bodily functioning, suggesting that hypochondriasis is not more prevalent among them and that they may actually appraise their health more optimistically than do younger people (6–10). It has been reported that hypochondriasis is present in 0.4%–14.0% of general medical patients (11–13), and prevalence estimates for the elderly vary between 3.9% and 33.0% (14, 15). The peak age periods for onset of the disorder have been reported to be adolescence, the fourth and fifth decades, and after age 60 (1, 2, 7, 12, 14, 16).

Some of the current confusion stems from methodological problems inherent in this research. These include lack of consensus on the definition and diagnostic criteria for hypochondriasis; failure to distinguish hypochondriasis as a psychiatric disorder from isolated hypochondriacal symptoms or somatization in general; and confounding factors that may mediate between age and hypochondriasis, such as medical morbidity, life stress, and depression.

Since medical morbidity increases with age, increases in somatic complaints, fear of disease, and preoccupation with the body in elderly persons could reflect a decline in objective health status more than hypochondriacal concerns (17). In addition, the elderly experience more benign dysfunction and diminishing physiological capacity, and these could foster concerns about debility, bodily decline, and illness. Indeed, it has been suggested that the elderly tend to misattribute these normative changes of longevity to serious medical disease (7, 18). Finally, some of the medical diseases of the elderly, such as organic brain syndromes, may be specific causes of hypochondriasis (1, 19).

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At all ages, life change and stress produce emotional distress and precipitate "functional" somatic symptoms and concerns about health. The elderly, of course, undergo many life stresses, particularly loss of status and income, death of a spouse, retirement, relocation, and social isolation. Hypochondriasis has been viewed as an attempt to cope with such stresses by taking on the role of a sick person (2, 20). This sort of reactive hypochondriasis, especially in response to social isolation and decreasing environmental stimulation, therefore could be more common among the elderly (2, 12, 21).

Depression is another possible confounding factor in the relation between aging and hypochondriasis. "Somatized" or "masked" depression may be relatively more common among the elderly than among those who are younger (22–25), and hypochondriasis in the elderly is often a secondary feature of an underlying depression (26, 27). Increased monitoring of normal physiology, increased incidence of physical illness, and lowered expectations regarding normative good health may all combine to heighten the older person's tendency to somatize depression (7).

The aim of this study was to examine the relation between age and hypochondriasis while taking into account the possible confounding influences of medical morbidity, social isolation, and depression.

## METHOD

The study was conducted in the general medicine clinic of the Massachusetts General Hospital. The clinic serves 29,000 patients who make more than 50,000 visits annually. It is staffed by 36 attending physicians and 65 house officers, all of whom provide primary rather than specialty medical care. Only the patients of attending physicians were studied. Patients were eligible if their cases had been followed at the hospital for at least 24 months and they had made at least one previous visit to the same physician. The exclusion criteria were illiteracy, inability to speak English, and major sensory or communication deficits.

Consecutive patients attending the clinic on randomly selected days completed a screening questionnaire for hypochondriasis. Those whose scores were above a predetermined cutoff level and a random sample of those whose scores were below that level completed a research battery consisting of self-report questionnaires, structured and semistructured interviews, and perceptual and cognitive tests. A structured diagnostic interview for hypochondriasis was included, and this was used for the *DSM-III-R* diagnosis of hypochondriasis. This interview was administered by a research assistant with a master's-level degree who was blind to the patient's screening score. The patient's medical record was then audited, and the primary physician, who was blind to the research data, completed a questionnaire about the patient. Each subject received $40 for participating.

**TABLE 1. Characteristics of *DSM-III-R* Hypochondriacal Subjects and Comparison Subjects**

| | Hypochondriacal Group (N=60) | | Comparison Group (N=100) | |
|---|---|---|---|---|
| Characteristic | N | % | N | % |
| Age (years)[a] | | | | |
| <45 | 17 | 28.3 | 21 | 21.0 |
| 45–64 | 21 | 35.0 | 36 | 36.0 |
| 65–74 | 16 | 26.7 | 32 | 32.0 |
| ≥75 | 6 | 10.0 | 11 | 11.0 |
| Female sex | 46 | 76.7 | 71 | 71.0 |
| Social class | | | | |
| I and II (highest) | 12 | 20.0 | 37 | 37.0 |
| III | 19 | 31.7 | 20 | 20.0 |
| IV and V (lowest) | 29 | 48.3 | 43 | 43.0 |
| Race | | | | |
| Black[b] | 9 | 15.0 | 5 | 5.0 |
| White | 50 | 83.3 | 94 | 94.0 |
| Asian | 1 | 1.7 | 1 | 1.0 |
| Marital status | | | | |
| Married | 29 | 48.3 | 62 | 62.0 |
| Separated | 4 | 6.7 | 0 | 0.0 |
| Divorced | 6 | 10.0 | 13 | 13.0 |
| Widowed | 9 | 15.0 | 11 | 11.0 |
| Never married | 12 | 20.0 | 14 | 14.0 |
| Regular church attendance | 21 | 35.0 | 49 | 49.0 |

[a] Mean±SD age of the hypochondriacal group, 55.7±16.1 years; of the comparison group, 58.6±14.9 years.

[b] Significant difference between groups ($\chi^2$=3.53, df=1, p=0.05).

Hypochondriacal symptoms were assessed with two self-report questionnaires, the Whiteley Index and the Somatic Symptom Inventory. The Whiteley Index (28) consists of 13 items on three subscales: disease fear, disease conviction, and bodily preoccupation. Its test-retest reliability and discriminant and convergent validity have been established (11, 28–31). The intrascale consistency of the Whiteley Index in this study was 0.94 (Cronbach's alpha), and the test-retest reliability was 0.84 (Pearson's product-moment correlation). Hypochondriacal somatic complaints were assessed with the 26-item Somatic Symptom Inventory, which is composed of items drawn from the MMPI hypochondriasis subscale and the Hopkins Symptom Checklist somatization subscale (32–34). This instrument had a test-retest reliability of 0.86 (Pearson's product-moment correlation) and an intrascale consistency of 0.93 (Cronbach's alpha). In previous work, the Whiteley Index and the Somatic Symptom Inventory were highly intercorrelated and together identified medical outpatients with a syndrome that is consistent with *DSM-III* hypochondriasis (31).

The clinical diagnosis of hypochondriasis was made with a structured diagnostic interview based on *DSM-III-R* criteria. This interview has acceptable interrater reliability and convergent and predictive validity (which are the subject of a separate report [35]; details are available from the first author on request).

Psychiatric disorder was assessed with the Diagnostic Interview Schedule (36), version III-A. This is a

**TABLE 2. Symptom Scores of *DSM-III-R* Hypochondriacal Subjects and Comparison Subjects Above and Below 65 Years of Age**

| Measure | Score (range=1–5)[a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Hypochondriacal Group | | | | Comparison Group | | | |
| | Subjects <65 Years Old (N=38) | | Subjects ≥65 Years Old (N=22) | | Subjects <65 Years Old (N=57) | | Subjects ≥65 Years Old (N=43) | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Total hypochondriasis score | 3.25 | 0.76 | 2.99 | 0.82 | 1.57 | 0.43 | 1.43 | 0.55 |
| Disease fear subscale | 3.06 | 1.07 | 2.61 | 1.10 | 1.52 | 0.56 | 1.35 | 0.46 |
| Disease conviction subscale | 3.14 | 1.08 | 2.71 | 0.93 | 1.37 | 0.48 | 1.29 | 0.59 |
| Bodily preoccupation subscale | 3.58 | 0.87 | 3.58 | 0.90 | 1.84 | 0.63 | 1.71 | 0.88 |
| Total Somatic Symptom Inventory score | 2.66 | 0.75 | 2.90 | 0.55 | 1.69 | 0.48 | 1.63 | 0.61 |

[a] Higher scores indicate greater pathology.

highly structured diagnostic interview that has been widely used; it generates psychiatric diagnoses in conformity with *DSM-III* nosology. It assesses most of the major axis I diagnoses (not including hypochondriasis), both current and lifetime, and is scored by computer. For all analyses, the diagnoses of psychosexual dysfunction, posttraumatic stress syndrome, and tobacco dependence were omitted.

Aggregate medical morbidity was assessed in several ways. First, the patient's medical record was audited, and the seriousness of every medical diagnosis was weighted (major, moderate, minor, or nonspecific symptoms) according to explicit predetermined criteria. This method was shown to have adequate interrater reliability. For these analyses we used separate counts of the number of major and moderate diagnoses. Second, the patient's physician rated the patient's current morbidity and future prognosis on a 5-point ordinal scale.

Life stress was not measured directly. However, several measures of social isolation were obtained. First, marital status was determined; second, patients were asked whether they attended church regularly; third, the social activity subscale of the Functional Status Questionnaire (37) was used to measure social integration. This last instrument consists of three questions, rated on an ordinal scale from 1 to 6, about social interactions, friends, and relatives. This questionnaire is a valid and reliable self-report instrument developed for use with ambulatory populations (37). It is scored by computer, which provides a numerical rating from 1 to 100 (maximal functional ability).

Somatosensory amplification, the self-reported sensitivity to a variety of unpleasant but nonpathological bodily sensations, was measured with the Somatosensory Amplification Scale, an 11-item questionnaire developed in previous work (38, 39). Responses are scored on a 5-point ordinal scale. In this study the questionnaire was found to have an intrascale reliability of 0.78 (Cronbach's alpha). It had a test-retest reliability of 0.79 (Pearson's product-moment correlation) over a mean interval of 74 days.

Statistical analyses included t tests and analysis of variance and covariance for continuous and ordinal data. The chi-square test was used for categorical data. Zero-order Pearson correlations were computed to estimate the association between pairs of variables; multivariate regression was used to determine the association between an outcome variable and two or more predictor variables. Analyses were done with the SAS for personal computers (40).

## RESULTS

Two thousand five hundred ninety-eight patients were approached and asked to participate in the study. One thousand three hundred eighty-nine (53.5%) of them met the inclusion criteria, consented to participate, and completed the screening questionnaires. One hundred thirty (9.4%) of these patients exceeded the cutoff score on the hypochondriasis screening questionnaire, of whom 60 (46.2%) were diagnosed as having *DSM-III-R* hypochondriasis according to the structured diagnostic interview. These 60 patients constituted the hypochondriacal group. One hundred eighty-seven patients were randomly selected from those who scored below the cutoff level on the screening test, and 100 (53.5%) of them were willing to complete the research battery. They constituted the comparison group.

When the hypochondriacal subjects were compared with the random group of nonhypochondriacal subjects, the two groups did not differ significantly in mean age or age distribution (table 1). They also did not differ significantly in other sociodemographic descriptors, except that there was a larger proportion of black patients in the hypochondriacal group, even after social class and educational level were controlled for. The hypochondriacal patients also had a significantly lower mean±SD score on the measure of social activity (61.2±31.7 versus 89.9±20.9; $t=6.9$, $df=158$, $p<0.001$).

We next examined the relation between age and hypochondriacal phenomenology. When the hypochondriacal subjects aged 65 years and over and those aged

**TABLE 3. Medical and Psychiatric Morbidity and Functional Status of *DSM-III-R* Hypochondriacal Subjects and Comparison Subjects**

| | Hypochondriacal Group | | | | | | Comparison Group | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Subjects <65 Years Old (N=38) | | Subjects ≥65 Years Old (N=22) | | Significance | | Subjects <65 Years Old (N=60) | | Subjects ≥65 Years Old (N=40) | | Significance | |
| Measure | Mean | SD | Mean | SD | t (df=58) | p | Mean | SD | Mean | SD | t (df=98) | p |
| Medical morbidity | | | | | | | | | | | | |
| Physician rating | | | | | | | | | | | | |
| Current medical status[a] | 2.32 | 0.96 | 2.95 | 1.17 | −2.3 | 0.03 | 2.22 | 1.08 | 2.74 | 1.02 | −2.4 | 0.02 |
| Prognosis[a] | 2.26 | 1.00 | 3.23 | 1.27 | −3.2 | 0.002 | 2.46 | 1.18 | 3.21 | 1.17 | −3.1 | 0.003 |
| Medical record audit | | | | | | | | | | | | |
| Number of major medical diagnoses | 0.45 | 0.89 | 1.50 | 1.65 | −2.8 | 0.01 | 0.80 | 1.18 | 1.20 | 1.74 | −1.4 | n.s. |
| Number of moderate medical diagnoses | 2.34 | 1.51 | 4.14 | 2.75 | −2.8 | 0.01 | 2.27 | 1.96 | 3.70 | 1.96 | −3.6 | 0.001 |
| Psychiatric morbidity | | | | | | | | | | | | |
| Number of anxiety disorders | 1.16 | 0.75 | 1.27 | 0.83 | −0.5 | n.s. | 0.62 | 0.87 | 0.43 | 0.71 | 1.2 | n.s. |
| Number of depressive disorders | 0.95 | 0.84 | 0.73 | 0.88 | 1.0 | n.s. | 0.35 | 0.68 | 0.33 | 0.66 | 0.2 | n.s. |
| Total number of psychiatric diagnoses | 1.82 | 1.45 | 1.55 | 0.91 | 0.9 | n.s. | 0.98 | 1.08 | 0.65 | 0.83 | 1.6 | n.s. |
| Total number of psychopathological symptoms | 33.42 | 18.33 | 28.73 | 10.09 | 1.3 | n.s. | 16.45 | 11.21 | 13.75 | 10.34 | 1.2 | n.s. |
| Social activities rating[b] | 69.7 | 25.1 | 46.5 | 36.8 | 2.6 | 0.01 | 92.7 | 17.9 | 85.7 | 24.4 | 1.6 | n.s. |
| Disability | | | | | | | | | | | | |
| Basic activities rating[b] | 83.0 | 19.4 | 64.1 | 27.6 | 3.1 | 0.003 | 94.9 | 11.8 | 91.7 | 15.9 | 1.1 | n.s. |
| Intermediate activities rating[b] | 65.4 | 26.1 | 44.6 | 23.0 | 3.1 | 0.003 | 84.3 | 21.0 | 75.9 | 24.7 | 1.8 | n.s. |
| Somatosensory Amplification Scale score[a] | 2.63 | 0.68 | 2.94 | 0.62 | −1.7 | n.s. | 2.02 | 0.53 | 1.94 | 0.56 | 0.67 | n.s. |
| Patient-rated health and care | | | | | | | | | | | | |
| Global health[a] | 2.58 | 0.75 | 2.27 | 0.74 | 1.5 | n.s. | 3.78 | 0.69 | 3.98 | 0.81 | −1.3 | n.s. |
| Effectiveness of medical care[a] | 3.13 | 1.02 | 3.09 | 1.15 | 0.14 | n.s. | 4.10 | 1.02 | 4.65 | 0.53 | −3.5 | 0.001 |

[a] Possible scores range from 1 to 5; higher scores indicate greater pathology.
[b] Possible scores range from 0 to 100; higher scores indicate better functioning.

under 65 were compared (table 2), the elderly group did not have more symptoms; indeed, they tended to have lower scores on disease fear and disease conviction, although these differences were not statistically significant. Similarly, within the comparison group (i.e., among the patients who were not clinically hypochondriacal), isolated hypochondriacal symptoms were fewer in the elderly, although not significantly so.

Table 3 presents the values for the potentially confounding variables in the relation between hypochondriasis and age. Within the hypochondriacal group, the elderly subjects emerged as sicker medically (both by physician rating and by medical record audit) but did not have a higher prevalence of depressive disorders (major depression, dysthymia) or anxiety disorders (generalized anxiety disorder, panic disorder, phobia). Their aggregate psychopathology was slightly lower than that of the younger subjects, but the difference was not statistically significant. More of the elderly hypochondriacal patients attended church regularly (younger group, 23.7%, N=9; elderly group, 54.5%, N=12; t=−2.5, df=58, p=0.02), but they had lower social activity scores than the younger hypochondriacal patients. They also reported higher rates of disability. Self-rated global health status did not differ between the age groups. Within the comparison group, medical morbidity was higher in those over 65 years of age, whereas psychiatric morbidity was not significantly different in the two age groups. Social activities and disability did not differ between the two age groups of comparison patients, although more of the older patients attended church regularly (younger group, 40.0%, N=24; elderly group, 62.5%, N=25; t=−2.2, df=98, p=0.03). As in the hypochondriacal group, the older patients in the comparison group did not rate their overall health status as significantly worse than did the younger patients.

## DISCUSSION

Hypochondriasis can refer both to a specific clinical disorder that is found in only a few individuals and to a nonspecific symptom that need not be psychopathological and occurs in many people. In this study we examined both, obtaining a sample of patients who met the *DSM-III-R* criteria for the disorder and also assessing hypochondriacal symptoms in a random sample of the rest of the clinic patients.

The hypochondriacal patients as a group were not older than the rest of the patients in the same medical clinic. Within this group, the patients who were 65 years of age and over did not differ significantly from those under 65 in disease conviction, disease fear, bodily preoccupation, or somatic symptoms. When we examined the comparison group, the patients who were aged 65 and over did not report more hypochondriacal symptoms or more functional somatic complaints than those under 65. These findings contradict the stereotype of the elderly as ruminative about their health and physiological functioning and preoccupied with inconsequential symptoms.

It should be noted that the bodily symptoms that make up the somatization scale can result from organic disease as well as from psychological distress. While the scale generally reflects psychiatric dysphoria rather than serious medical disorder, any of these somatic symptoms can be caused by the latter, and this is more likely in a medically ill population. We did not determine whether individual somatic symptoms could be attributed to medical disease; we only measured total somatization and aggregate medical morbidity. The somatization questionnaire results and the number of major medical diagnoses were correlated in the comparison group ($r=0.29$, $df=98$, $p=0.006$) but were not significantly associated in the hypochondriacal group.

It has been suggested that the elderly are more sensitive to benign bodily dysfunction and normal physiological processes, which they then misattribute to disease, mistaking them as evidence of a pathological process rather than of longevity. The Somatosensory Amplification Scale appraises the respondent's sensitivity to a range of unpleasant but nonpathological visceral and somatic sensations, such as hunger, loud noise, and temperature extremes. Older patients, whether they had diagnoses of hypochondriasis or not, did not score significantly higher than younger patients on this scale.

The elderly and the younger patients also did not differ in their overall feeling of healthiness, i.e., in global self-ratings of their health status. In both groups of patients, the responses to the items "Feeling you are not in as good physical health as most of your friends," "In general how do you rate your present physical health?" and "How do you feel about your health?" did not vary significantly with age. This is in accord with reports that age is either independent of or only weakly related to global self-ratings of health (41).

What about the confounding variables thought to mediate in the relation between hypochondriasis and aging? In this study, medical morbidity was significantly higher in the elderly. Our data thus suggest that age was not associated with an increase in hypochondriacal symptoms despite the finding that older patients had more medical illness.

Social isolation was assessed with data on marital status, regular church attendance, and social activities. While marital status did not differ between the age groups, the elderly hypochondriacal patients reported more difficulty participating in social activities than did the younger hypochondriacal patients. The elderly hypochondriacal patients also reported more difficulty performing basic and intermediate activities of daily living than did the younger ones. Perhaps hypochondriacal patients' worries, demands, complaints, and self-centered style increasingly hinder social integration, friendships, and contact with family as they age; significant others may drift apart from their hypochondriacal friends and become less tolerant of them over time. All of these measures of dysfunction, of course, are also related to medical status, and the elderly patients were sicker. It may be that some observers have mistakenly considered the elderly to be more hypochondriacal because they are less functional and more disabled and that they have misattributed elderly persons' disability to hypochondriacal concerns about their health rather than to objective medical disease.

When we compared the hypochondriacal group with the comparison group, we found that functioning declined with age only in the hypochondriacal subjects. These elevated levels of disability were not the result of differences in medical morbidity, since the aggregate medical morbidity of the hypochondriacal group was not significantly greater than that of the comparison group (42). In general, disability was prominent among the hypochondriacal subjects (13). More than half of them reported serious impairment in intermediate activities and social functioning, and one-fourth of them were not working because of health problems (13).

Finally, psychiatric morbidity in general and depression in particular were no more prevalent in patients who were 65 years of age and over. We found no associations among old age, depression, and hypochondriasis. Psychiatric morbidity in general was, however, significantly greater in the hypochondriacal than in the comparison patients. This difference persisted at all ages and for a number of disorders, including major depression ($\chi^2=10.5$, $df=1$, $p<0.01$), dysthymia ($\chi^2=13.9$, $df=1$, $p<0.01$), and generalized anxiety disorder ($\chi^2=27.95$, $df=1$, $p<0.001$) (details available from the first author on request).

Thus, hypochondriasis, viewed both as a diagnosable clinical disorder and as a nonspecific symptom found to some degree in all patients, appears to be unrelated to age. Are there alternative explanations for these findings? First, it is possible that hypochondriasis is more prominent in extremely old individuals (those over 75 years of age, for example) and that our groups did not contain enough "old old" patients to disclose this relationship. Second, the younger patients may have been a biased group. It could be that the younger patients who seek help at an academic medical center such as ours are unusually concerned about their health. If so, a higher prevalence rate of hypochondriasis among the elderly would be obscured because they were being compared to an unrepresentative sample of younger patients, namely, those who are unusually hypochondriacal. This seems somewhat unlikely, however.

This study, because it was cross-sectional in design, did not address the question of whether individuals become more or less hypochondriacal, or evaluate their health differently, as they age. These answers await longitudinal, prospective studies that will follow the same cohort of individuals as they grow older.

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# Absence of Cognitive Impairment After More Than 100 Lifetime ECT Treatments

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*The cognitive function scores and subjective memory complaints of eight patients who had each received more than 100 treatments with bilateral modified sine wave ECT were equivalent to those of matched patients who had never received ECT. The results suggest that patients given many ECT treatments over several courses do not manifest measurable cognitive impairment at long-term follow-up.*

(Am J Psychiatry 1991; 148:929–932)

Cognitive impairments after a series of ECT have been well characterized (1). After ECT, many patients have anterograde and retrograde memory deficits that typically resolve within a few months after treatment (2). Permanent effects appear to be restricted to gaps in memory for events that transpired during the months surrounding the ECT course (2). Nonetheless, at long-term follow-up a small minority of patients report profound cognitive deterioration, which they attribute to ECT, although objective neuropsychological evaluations may not reveal significant deficits (2, 3).

Virtually all modern studies of ECT cognitive effects have involved patients who were each given a single course of ECT (2). Early studies with patients who received large numbers of ECT treatments suffered from a number of methodological problems: nonblind evaluation of ECT patients and comparison subjects (4, 5), group differences in severity of psychopathology, lack of clarity as to whether a prolonged single course or multiple courses of ECT were administered (4, 5), and use of inappropriate instruments for neuropsychological evaluation. In this early work, the patients were predominantly treated with unmodified ECT and their own perceptions of their cognitive functioning were not studied. In a controlled comparison, we gathered preliminary information on the severity of cognitive deficits and subjective memory complaints in patients who had received more than 100 treatments with bilateral modified sine wave ECT in their lifetimes.

## METHOD

The study was conducted at a large state facility in rural upstate New York. All living patients who had received more than 100 ECT treatments at the facility between 1965 and 1990 were identified. These 10 patients constituted less than 1% of the patients who had been administered ECT during the 25-year period. Nine of these 10 patients were still followed at the facility at the time of study. Eight of them agreed to participate; the remaining patient was experiencing a manic episode and was not recruited for participation. The eight ECT patients were individually matched to eight patients who had never received ECT; matching was based on age, sex, psychiatric diagnosis, inpatient/outpatient status, and specific ward or outpatient clinic.

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**TABLE 1. Demographic Characteristics and Cognition Scores for Eight Patients Given More Than 100 Lifetime ECT Treatments and Matched Patients Never Given ECT**

| Variable | ECT Group Mean | ECT Group SD | Comparison Group Mean | Comparison Group SD | Paired t Test (df=7) |
|---|---|---|---|---|---|
| Descriptive variables | | | | | |
| Age (years) | 58.1 | 12.1 | 58.5 | 13.0 | 0.34 |
| Education (years) | 10.3 | 2.3 | 11.8 | 3.3 | 0.83 |
| Age at onset (years) | 21.5 | 8.8 | 42.6 | 13.5 | 2.87[a] |
| Number of psychiatric hospitalizations | 19.2 | 13.8 | 3.9 | 3.2 | 3.27[a] |
| Lifetime number of ECTs | 160.1 | 58.8 | | | |
| Number of ECT courses | 11.8 | 4.8 | | | |
| Months from last ECT to evaluation | 38.7 | 41.3 | | | |
| Psychopathology scores | | | | | |
| BPRS | 30.9 | 9.6 | 26.0 | 5.7 | 2.64[a] |
| Montgomery-Asberg depression scale | 11.3 | 10.6 | 6.1 | 3.3 | 1.71 |
| Cognition scores | | | | | |
| Mini-Mental State total | 26.6 | 3.3 | 26.5 | 4.3 | 0.08 |
| Buschke Selective Reminding Test (six trials) | | | | | |
| Total recall | 34.8 | 12.4 | 37.1 | 9.8 | 0.50 |
| Delayed recall | 6.1 | 3.3 | 5.6 | 3.1 | 0.41 |
| Recognition | 11.5 | 0.9 | 10.8 | 2.0 | 0.89 |
| Subjective memory questionnaire | | | | | |
| Events long ago | 3.5 | 1.3 | 3.9 | 1.0 | 0.70 |
| Events a few minutes ago | 3.8 | 0.7 | 3.9 | 0.9 | 0.31 |
| Names and faces of people | 3.6 | 0.5 | 3.9 | 1.0 | 0.61 |
| Events a month from now | 3.1 | 0.8 | 3.7 | 0.7 | 1.93 |
| Global | 3.4 | 0.7 | 4.0 | 0.9 | 1.49 |
| Sum of five items | 17.4 | 3.0 | 19.4 | 3.7 | 1.32 |

[a] $p<0.05$.

Each group contained three men and five women; three were inpatients and five were outpatients. Other descriptive characteristics of the patients are presented in table 1. The patients in both groups belonged to three diagnostic categories: bipolar disorder (N=2), unipolar major depression (N=2), and schizophrenia (N=4). The groups did not differ in descriptive features except that the ECT group had histories of more severe, recurrent illness, a significantly earlier onset, and significantly more psychiatric hospitalizations. The patients in the ECT group also had significantly more severe symptoms, according to Brief Psychiatric Rating Scale (BPRS) scores, at the time of evaluation (table 1).

All ECTs had been administered with a Medcraft sine wave device and bilateral frontotemporal electrode placement. The standard ECT procedure involved use of thiopental sodium, succinylcholine chloride, and oxygenation. At the time of evaluation, all patients were receiving psychotropic medications, and the regimens of the two groups were comparable: five patients in each group were taking high-potency antipsychotics; three ECT patients were taking antidepressants (nortriptyline, amoxapine, and fluoxetine, respectively), as were two non-ECT patients (nortriptyline and doxepin, respectively); three ECT patients and four non-ECT patients were taking benztropine or trihexiphenidyl hydrochloride; and four ECT patients and three non-ECT patients were taking lithium. None was receiving benzodiazepines.

After giving informed consent, the patients were evaluated by one of two physicians, a research psychiatrist (D.P.D.) or a fellow in geriatric psychiatry (F.T.), who was blind to assignment to the ECT or comparison group. Each patient completed a subjective memory questionnaire, an abbreviated version of the memory rating of Squire et al. (6). The five questions selected inquired about the patient's assessment of long-term memory, recent memory, memory for names and faces, anterograde memory, and global memory before the first psychiatric hospitalization. Each answer was given on a 5-point scale (1=much worse, 5=much better). Three additional questions inquired about the patient's perceptions of the effects of ECT, medication, and psychotherapy on global memory. The patients were also given the Mini-Mental State examination (7) and the Buschke Selective Reminding Test (8). The Buschke test involves six trials of a 12-item list, followed by testing of recall and recognition after a 15-minute delay. The blind rater also completed the Montgomery-Asberg Depression Rating Scale (9) to evaluate depressive symptoms and the BPRS to index global psychopathology. For a particular patient, all assessments were conducted by one rater. Before the study, the two raters established reliability for the Montgomery-Asberg depression scale and the BPRS with an independent group of six patients (intraclass correlation coefficients for fixed raters, 0.78 and 0.89 for the Montgomery-Asberg and BPRS total scores, respectively).

Because one-to-one matching was used, the statistical analyses were based on paired observations. Given the limitations on power due to the small number of subjects and the importance of identifying group differences that did not quite reach significance, the significance levels were not adjusted for the number of statistical comparisons performed.

## RESULTS

The two groups did not differ in any measure of objective or subjective cognitive functioning (see table 1). The mean total Mini-Mental State scores of the two groups were identical and indicated normal functioning for this age range (7). The groups did not differ on any of the Mini-Mental State subscales, including short-term recall. Likewise, the groups did not differ in scores on any of the Buschke test measures, including long-term storage, consistency of long-term recall, and number of intrusions. Neither total Mini-Mental State score nor Buschke test scores were significantly related to age, sex, or education. Across the groups ($N=16$), greater psychopathology was associated with poorer cognitive performance (BPRS and Mini-Mental State: $r=-0.63$, $p<0.01$; BPRS and Buschke total recall: $r=-0.51$, $p<0.05$; Montgomery-Asberg scale and Mini-Mental State: $r=-0.47$, $p<0.1$; Montgomery-Asberg scale and Buschke total recall: $r=-0.53$, $p<0.05$), and these correlations were similar when the two groups were examined separately. Repeated measures analyses of covariance were conducted separately for the total Mini-Mental State and Buschke total recall scores; patient group was used as the repeated measures term, and BPRS score was used as a covariate. For both total Mini-Mental State and Buschke total recall, there was no effect of patient group; the covariate-adjusted mean score on the Mini-Mental State indicated nonsignificantly better cognitive performance in the ECT group (27.6) than in the non-ECT group (25.6).

On the subjective memory complaint questionnaire, the two groups did not differ significantly in any of the individual items or in the overall mean score on the five items. In the subjective reports on effects of treatments, two patients indicated that ECT had worsened their memory, two reported no change, and four stated that ECT had improved their memory. Subjective reports on the effects of psychotropic medication and psychotherapy were similar in the two groups (one patient in each group reported never having received psychotherapy).

## DISCUSSION

There has been little information on the long-term cognitive consequences of multiple courses of modified ECT involving large numbers of treatments. We found that a small group of patients who had received on average 12 ECT courses, involving 160 treatments, could not be distinguished from a carefully matched psychiatric comparison group on either objective or subjective measures of cognitive function. Of note, both patient groups had Mini-Mental State scores within the established range for psychiatric patients (7). Both bilateral electrode placement and sine wave stimulation are known to produce greater acute and subacute cognitive impairments than other forms of ECT (2). Therefore, the large number of treatments administered and the form of ECT used should have increased the likelihood of observing group differences had ECT resulted in long-term adverse cognitive effects. The ECT group was blindly assessed months to several years after the last ECT. These findings suggest that the administration of a large number of ECT treatments, spaced over several courses, does not result in long-term cognitive impairment.

This conclusion should be tempered by the limitations of this study. The small number of subjects, necessitated by the rarity of patients who receive more than 100 ECT treatments, may have limited the likelihood of establishing group differences because of lack of statistical power. However, after we adjusted for level of symptoms (BPRS scores), the ECT group had nonsignificantly better objective cognitive performance than the comparison group. Another limitation concerns the range of cognitive functions examined. The Mini-Mental State provides a gross measure of global cognitive function and has shown particular utility in the assessment of dementing conditions (7). The Buschke test examines anterograde learning and memory. It is conceivable that cognitive domains not evaluated by these instruments are subject to long-term ECT effects. However, these two instruments evaluate domains that are known to be impaired immediately after ECT (2), and more comprehensive evaluations of patients who received single courses have failed to identify persistent deficits several months after ECT (1, 2). This suggests that broader assessment is unlikely to reveal long-term adverse effects in the type of patients studied here. The findings pertain to patients who have received large numbers of treatments, distributed over several courses. It is unknown whether they apply to patients who receive an unusually large number of treatments within a single course, although other investigators have reported the absence of cognitive impairment at long-term follow-up of schizophrenic patients treated with "regressive" ECT (10). Further, we cannot exclude the possibility that the patients in our study were selected to receive multiple courses of ECT in part because they showed acceptable levels of cognitive side effects earlier in their treatment histories.

Only a small proportion of former ECT patients report long-term adverse cognitive effects, and there may be a number of factors that contribute to these perceptions other than treatment-induced cognitive changes (2, 3). Research of the type exemplified here cannot rule out the possibility that a few individuals experience long-term adverse effects. Rather, these findings document that with markedly intense exposure to ECT such long-term impairment, if it occurs at all, is uncommon.

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# Technique for Greatly Shortening the Transition From Methadone to Naltrexone Maintenance of Patients Addicted to Opiates

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*Acute methadone detoxification was induced by the intravenous administration of naloxone during simultaneous intravenous sedation with midazolam, a fully reversible short-acting benzodiazepine, in seven patients addicted to opiates. Within hours the patients tolerated full doses of naltrexone. This technique enables patients to transfer easily, quickly, and safely from methadone to naltrexone maintenance.*

(Am J Psychiatry 1991; 148:933–935)

Many opiate addicts genuinely want to become opiate free, but traditional withdrawal techniques result in high rates of dropout and early relapse. Severe objective and subjective withdrawal symptoms usually continue for at least several days and are strongly related to anxiety (1). Repeated low doses of naloxone have been used (1, 2), but this technique reduces the duration rather than the severity of withdrawal distress. Despite this drawback, some addicts find this approach attractive (3). Clonidine and naltrexone have been used for rapid transition to naltrexone maintenance (4, 5). Recently, we demonstrated that the acute withdrawal-precipitating action of naloxone in opiate addicts can be blocked by barbiturate anesthesia and that the continued administration of naloxone followed by naltrexone maintains the complete suppression of withdrawal distress after the initial high loading (6).

The aim of this clinical trial was to see whether rapid antagonist-precipitated opiate detoxification techniques (1, 6) can be safely modified so as to reduce the need for specially trained staff and sophisticated and expensive equipment while preserving the low levels of distress that make withdrawal a less unattractive option to addicts.

## METHOD

Seven patients with diagnoses of opioid dependence according to the *DSM-III-R* criteria gave informed consent to participate in this clinical inpatient study. The patients (three female and four male) had 3- to 13-year histories of opiate addiction (mean±SD=7.8±3.6 years). Their ages ranged from 20 to 36 years (mean±SD age=27.2±4.9 years). No drugs other than opiates were detected in their urine during the 2 months prior to the study. All were in good health, as determined by physical examinations and routine laboratory tests. They had been on a *dl*-methadone hydrochloride maintenance regimen for at least 12 days (dose range=40–120 mg/day; mean±SD dose=72.8±26.2 mg/day). They received their daily doses of methadone under supervision at the drug-dependency outpatient clinic.

During the assessment period and the withdrawal program, severity and presence of withdrawal symptoms were rated once a day on a modified rating scale (7) that included the following: piloerection, tremor, perspiration, restlessness, lacrimation, yawning, cold and hot flashes, abdominal cramps, muscle twitches, rhinorrhea, and back pain. Following the example of Wang et al. (7), we gave these symptoms different weights and rated them as absent or present. Possible scores ranged from 0 to a maximum of 29.

Twenty-four hours after the last oral methadone intake, each patient was sedated by injection of a bolus of midazolam, 30 mg, into a peripheral vein. Within 10 minutes, 4 mg of naloxone diluted with 200 ml of 0.9% saline was injected by means of a constant infusion pump. Sedation was maintained as necessary with repeated injections of midazolam, 50–75 mg. Shortly after the naloxone infusion was completed, the patients received repeated doses of flumazenil, 2–6 mg, until they were fully awake. Opiate antagonist treat-

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**TABLE 1. Withdrawal Symptoms and Physical Signs in Seven Opiate Addicts Given Naloxone and Naltrexone During Detoxification From Methadone**

| | Hours Before and After Detoxification Procedure | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | −24 | | −1 | | +24 | | +48 | | +72 | | +96 | | +120 | |
| Measure | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Rating of severity of withdrawal distress[a] | 0.43 | 0.53 | 0.86 | 0.69 | 1.43 | 0.79 | 1.28 | 0.75 | 0.86 | 0.69 | 0.86 | 1.06 | 0.57 | 0.53 |
| Blood pressure (mm Hg) | | | | | | | | | | | | | | |
| Systolic | 110.7 | 7.3 | 107.8 | 9.0 | 118.6 | 12.1 | 115.7 | 5.3 | 114.3 | 8.3 | 111.4 | 4.7 | 111.4 | 9.4 |
| Diastolic | 68.5 | 6.9 | 68.5 | 12.1 | 68.6 | 6.3 | 74.3 | 13.9 | 72.8 | 9.5 | 70.0 | 5.7 | 67.1 | 7.5 |
| Pulse rate (bpm) | 79.3 | 10.6 | 74.3 | 7.9 | 72.8 | 9.5 | 68.6 | 6.9 | 77.8 | 5.6 | 71.4 | 8.5 | 77.1 | 8.5 |

[a] Scale of Wang et al. (7); range of possible scores=0–29.

ment was then continued with oral naltrexone, 50 mg/day, which was repeated every 24 hours until no more opiates were detected in urine samples. During the detoxification procedure, heart rate was recorded continuously by an automatic ECG, and blood pressure by an automatic cuff manometer. After starting the acute detoxification treatment, patients were examined every 8 hours by staff nurses to ascertain body temperature, blood pressure, and heart rate. To control the efficacy of the treatment, urine samples were analyzed daily for opiates, benzodiazepines, and other drugs of abuse.

Two patients chose to continue naltrexone maintenance after the end of the study.

## RESULTS

In this study the usual acute onset of withdrawal signs and symptoms following the intravenous administration of naloxone in unsedated opiate addicts (1, 2, 7) was completely suppressed by midazolam. In all of the patients, adequate individual methadone maintenance had completely suppressed withdrawal distress before detoxification. After the reversal of benzodiazepine sedation with flumazenil (8), no objective withdrawal symptoms were recorded on the rating scale (7) (table 1). The oral administration of 50 mg of naltrexone during and after naloxone administration did not lead to the reappearance of withdrawal symptoms. Mean scores on withdrawal symptoms, measured daily at 9:00 a.m. by the revised Wang et al. rating scale, showed no significant changes throughout the study (Duncan's multiple range test). It is noteworthy, however, that two subjects experienced mild perspiration (lasting for 4–6 hours) 48 hours after the detoxification process was initiated.

Heart rate, blood pressure, body temperature, body weight, and respiratory rate remained stable during the whole treatment period. Furthermore, no changes in routine clinical laboratory parameters could be detected in any of the patients. Before the patients were discharged, all of their urine samples were found to be free of opioids and benzodiazepines. Benzodiazepines were not found 48 hours after the administration of midazolam; methadone could be observed until 120 hours after the last intake.

All seven patients successfully completed detoxification, as verified by negative results on urine tests and pretreatment levels of withdrawal distress.

## DISCUSSION

In this study our previous experience with the effective suppression of withdrawal symptoms during continuous naloxone infusion (1) was confirmed. In other studies (2) high doses of naloxone produced acute and severe abstinence symptoms in opiate addicts after intravenous administration. The onset of withdrawal symptoms was often described as the only conditioning stimulus for relapse. As we showed in an earlier report (6), this dramatic effect of naloxone is prevented by general anesthesia. However, this technique has the drawback of requiring sophisticated medical care and technical equipment as well as specially trained staff. To develop a simpler treatment design, we chose a short-acting benzodiazepine, midazolam, which was equally effective in suppressing naloxone-precipitated withdrawal symptoms in these opiate addicts. The advantage of this new method is that it may be safer than general anesthesia, and the sedative effect of the benzodiazepine can be completely reversed by administering the antagonist flumazenil (8).

The reason for changing from naloxone to oral naltrexone after the patients awoke from sedation is the much longer pharmacological action of naltrexone. This drug is also much cheaper than naloxone. After anesthesia, withdrawal signs appear to be suppressed by the continuous presence of an adequate concentration of opiate antagonists in the blood. Our earlier findings (6) support the notion that the withdrawal syndrome may be suppressed by an effect of opiate antagonists on unblocked opiate receptor sites. This might also explain the protective action during steady-state naloxone in the presence of exogenous opiates. However, our experiences suggest that it is very important to exclude polydrug abuse, especially alcohol abuse, to avoid possible side effects (e.g., acute onset of delirium tremens) during use of the antagonist-precipitated opiate withdrawal technique.

This rapid and safe approach permits opiate detoxification to be greatly accelerated without any danger; it is also economical in terms of treatment costs and time away from work. It is attractive to drug addicts who are afraid of withdrawal distress. In the future, very long-acting opiate antagonists should be used after rapid detoxification to block opiate receptor sites for a longer time, so as to interrupt the vicious circle of addiction.

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# Blunting of Noradrenergic-Stimulated Growth Hormone Release in Mania

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*Seven drug-free patients with bipolar affective disorder, currently in a manic phase, underwent desipramine-induced growth hormone (GH) stimulation, as did seven healthy age- and sex-matched subjects. There was significant blunting of GH release in the manic patients, suggesting a down-regulation of $\alpha_2$-noradrenergic responses. Blunting of GH release was not related to severity of symptoms, duration of illness, or age. Similar blunting has previously been described in depressed patients.*

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Katakami et al. (1) have shown that $\alpha_2$-noradrenergic receptors in the arcuate nucleus of the hypothalamus indirectly control growth hormone (GH) release by increasing the release of GH-releasing hormone (GH-RH). Clonidine, when administered to healthy subjects, stimulates GH release by acting at these receptors (2, 3). The monoamine reuptake inhibitor desipramine blocks the reuptake of norepinephrine and, when given orally, has a similar action (4, 5). The effect is blocked by the $\alpha_2$-adrenergic antagonist yohimbine but not by the $\alpha_1$-adrenergic antagonist prazosin (6), which supports the involvement of $\alpha_2$ receptors.

GH responses to clonidine (7, 8) and to desipramine (5, 9, 10) are significantly blunted in both unipolar and bipolar depression. To our knowledge, such responses have not been investigated in mania, and they have considerable implications for our understanding of noradrenergic processes in the condition. We therefore decided to study desipramine-induced GH responses in unmedicated manic patients.

## METHOD

Seven inpatients (four women and three men) 18 to 70 years old (mean±SD=43.4±13.7), with bipolar affective disorder, who fulfilled *DSM-III-R* criteria for a current manic episode, participated. The diagnosis in each case was based on separate assessments by three clinicians, all of whom interviewed the patients and had access to their past medical records. (An additional patient was considered unsuitable because one of the clinicians disputed the diagnosis.) All patients gave written informed consent and were physically healthy as determined by physical examination, routine blood tests, and ECG. All were drug free for at least 8 weeks before the study. This was determined from the history and a urinary drug screen. Five patients had previously taken lithium; one, haloperidol; and one, amitriptyline. The comparison group consisted of seven healthy adults (four women and three men) without a previous or family history of psychiatric illness, who were 20 to 68 years old (mean±SD=40.5±11.6). Their social background was similar to that of the patients. The three premenstrual patients and three premenstrual healthy subjects were tested in the follicular phase of their menstrual cycle. The severity of symptoms was assessed on the day of testing with the 8-item rating scale of Peterson et al. (11). The mean±SD score was 20.1±2.0.

Tests were conducted as previously described (5). Briefly, an 18-gauge cannula was inserted into a forearm vein at 8:30 a.m. The subject was then allowed to relax for 20 minutes before blood was drawn for determination of GH levels. Two baseline 8-ml samples were collected at a 15-minute interval in lithium-heparin tubes; results from these two samples were averaged. Desipramine, 1 mg/kg of body weight, was then given orally. Subjects were encouraged to remain supine as much as possible but were allowed to walk around the room intermittently and talk as much as they wished. This was essential to ensure compliance in the case of the manic patients. Throughout the test subjects were accompanied by a nurse and a clinician. Blood for further GH determination was collected 90, 120, and 180 minutes after the administration of desipramine. GH was assayed (in a manner blind to diagnosis) by double-antibody radioimmunoassay (Diagnostic Products Corp., Los Angeles). Within- and between-assay coeffi-

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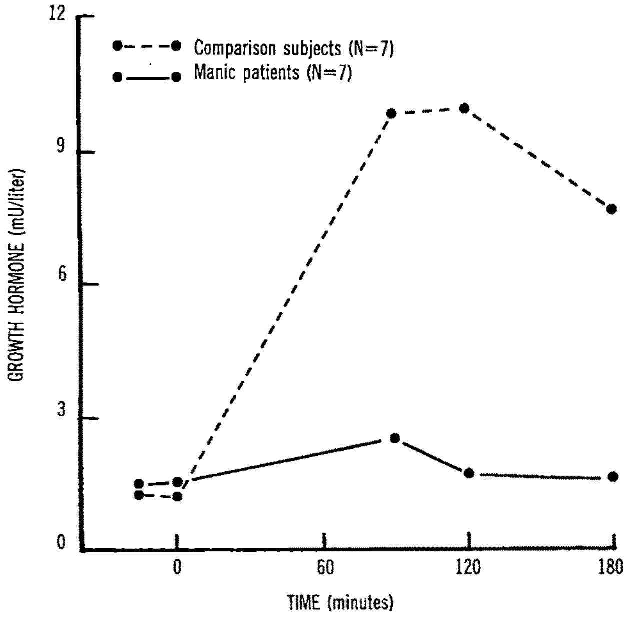
**FIGURE 1. Mean Growth Hormone Levels in Seven Manic Patients and Seven Normal Subjects Who Underwent Desipramine-Induced GH Stimulation[a]**



[a] Differences between the patients and the normal subjects were significant at 90 minutes and 120 minutes ($p<0.05$, Tukey's test).

cients of variation were 4% and 5%, respectively. Data were analyzed by means of two-way analysis of variance (ANOVA), Tukey's test, and Pearson product-moment correlation coefficients through use of Statgraphics (12).

## RESULTS

GH response was measured as the maximum GH value relative to baseline. The mean±SD GH response in the manic patients was 1.43±1.8 mU/liter, compared to 8.76±4.3 mU/liter in the healthy comparison subjects ($t=4.10$, $df=12$, $p<0.005$). A two-way ANOVA with repeated measures yielded the following: $F=20.19$, $df=5, 69$, $p<0.001$ (group: $F=50.1$, $df=1, 60$, $p<0.001$; time of sampling: $F=12.6$, $df=4, 60$, $p<0.001$). There was a significant Group by Time interaction ($F=9.5$, $df=4, 60$, $p<0.001$). Differences between the patients and the healthy subjects were significant at 90 minutes and 120 minutes ($p<0.05$, Tukey's test) (figure 1).

GH response was not related to patient age ($r=-0.44$, $df=5$, $p=0.31$), duration of illness ($r=-0.42$, $df=5$, $p=0.34$), or severity of symptoms as measured by the Peterson rating scale ($r=0.39$, $df=5$, $p=0.37$).

## DISCUSSION

There have been few reports of neuroendocrine challenge tests in manic patients. This undoubtedly relates to the fact that such tests are difficult to conduct in unmedicated manic patients. It took 2 years in a busy psychiatric unit to recruit the current group of seven patients with mild to moderately severe mania. The present study provides the first report of significant desipramine-induced GH blunting in such patients. Similar blunting has also been seen in patients with major depression and in such patients does not normalize with treatment (13).

Laakmann et al. (6) have provided convincing evidence that the action of desipramine in elevating GH levels is mediated by $\alpha_2$-noradrenergic receptors. If this is the case, it is likely that such receptors in mania are functionally down-regulated, as is the case in depression (2, 3, 5, 7, 8). It would thus seem improbable that the receptor alteration is a core etiological factor in either mental state. It is, however, an important marker for affective disorder, and such noradrenergic dysfunction may render the individual vulnerable to mood fluctuation.

Stein (14) was the first to put forward a comprehensive theory of mood disorder based on the putative behavioral function of noradrenergic neurons as a reward system. He postulated a noradrenergic deficiency theory of depression and a noradrenergic excess theory of mania. Although the present study focused on only one noradrenergic receptor subtype, the data provide little to support Stein's original hypothesis. It is highly unlikely that both noradrenergic deficiency and noradrenergic excess would have the same impact on $\alpha_2$-noradrenergic receptors.

The possibility exists that the aberrant responses are the result of previous exposure to psychotropic medication. We cannot rule out this possibility, but two of the patients were drug free for 8 weeks and the others for periods ranging from 6 to 12 months. The possibility that previous exposure to psychotropic medication would have long-lasting effects over this period is remote. It is of interest that two of the patients were previously studied during their first depressive episodes, when they were entirely drug naive, and on that occasion they had similar blunted responses (10), which supports the view that the abnormality is a trait marker in bipolar affective disorder.

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# Book Forum

## Nancy C. Andreasen, M.D., Ph.D., Editor

### AUTISM

**Autism: Developmental Clinical Psychology and Psychiatry, vol. 15,** *by Laura Schreibman. Newbury Park, Calif., Sage Publications, 1988, 176 pp., $19.95; $12.95 (paper).*

**Autism: Explaining the Enigma,** *by Uta Frith. Cambridge, Mass., Basil Blackwell, 1989, 288 pp., $19.95.*

Although most clinicians use standard diagnostic systems (*DSM-III, DSM-III-R,* and *ICD-10,* for example) to label a patient "autistic" or to include a subject in a research study of "autism," many, if not most, clinicians and researchers maintain independent beliefs about the nature of autism. Using a system and believing in its validity are quite separable. Current beliefs concerning the nature of autism sort into at least four camps: clinician centered, diagnostic system centered, deficit centered, and treatment centered.

Clinician-centered beliefs spring from the clinician's view that internalized experience allows one to make natural categories based on the accumulated knowledge of exemplars of the syndrome. Autism is recognized in the course of a clinical interview by individual practitioners. Formal diagnostic systems are seen as flexible guidelines for interpreting the syndrome. There could be as many "autisms" as there are clinicians.

System-centered beliefs arise when clinicians and researchers invest faith in the measurable reliability and validity of diagnostic interviews, inventories, or checklists to create the form of the syndrome. In system-centered beliefs, autism is best defined by a set of symptoms and behaviors that can be marked in sets of patients. The item sets serve as a basis for belief in the syndrome.

Deficit-centered beliefs emerge from theoretical notions of the possible causal bases for autism. Deficit-centered beliefs focus on the unifying force that hypothesizing a key deficit brings to any conceptualization of the syndrome. In fact, a large part of the history of the study of autism is essentially the history of shifting deficit-centered beliefs. Cold parents, faulty vestibular systems, impaired language development, and genes for disordered social cognition have all been claimed as unifying deficits.

In *Autism: Explaining the Enigma,* Uta Frith argues for the deficit-centered belief in autism as defined by a "weak drive for coherence" (p. 163). Frith argues that autism is a failure to create metarepresentations of elements of experience. For example, if you are asked to create a category of things with fur and you include a fur hat, a pet bunny, and the old bologna in the back of the refrigerator, you are creating a metacategory. You are imagining a togetherness of visually dissimilar elements, and you have created a framework that is metarepresentational.

Frith claims that the inability to generate metarepresentations defines autism, and that this unique deficit is part of the failure to extract global coherence from experience. In Frith's model, the social impairment of autistic individuals arises from an underlying failure to create imaginatively the abstraction (or metarepresentation) of the minds of others. In this model, if we do not attribute minds to others, we cannot predict their behavior and we cannot interact normally in social encounters.

Frith's model is an extension of the developmental theories of Leslie, Perner, and others who argued that the normal child's creation of a theory of mind is an innately determined step in the formation of a template for all social cognition. Frith's application of this theoretical model to the impairments of autism is attractive and intuitively appealing, and her arguments are coherent and well presented.

The only drawback to the use of this theoretical framework to define autism is that the model fails to explain the behaviors that arise very early in the development of many autistic individuals and often remain as part of their repertoire. These include an irritable response to tactile stimulation such as simple touching or holding, gaze aversion, the loss of first words or very early language skills, the presence of pica or other disordered taste preferences, bizarre reactions to pain, and sleep disorders. Such problems appear before the child is even 2 years old—before the normal expected point of the unfolding of the ability to form a theory of the mind of another. Even in cases where such behaviors are noted only later in development it cannot be argued that they are a consequence of cognitive impairment. For the Frith model, all such behaviors must represent nonpathognomonic symptoms. Some of these symptoms, however, suggest impairment to basic mammalian mechanisms of sociability, such as the ability to experience a reduction of tension (anxious arousal) by means of the touch of another.

Moreover, many high-functioning autistic children and adults do form ideas of the minds of others. In some autistic individuals such ideas may be mirrors of their own minds (such as expecting you to like the foods or hobbies they do), but in others the ideas of minds may be more sophisticated: these individuals will ask your preferences in cars or activities or television shows as if they expected an answer different from their own interests.

Conversely, retarded children with normal social interests, emotions, and social directedness have shown impaired ability to imagine the minds of others.

Frith's extended discussion of the "sensitivity" and "specificity" of this hypothesized deficit in imagining the minds of others is important for the field because it forces attention to social cognition in autism. However, despite the global nature of this hypothesized deficit, and despite the implications of such a deficit for social behavior, this deficit alone does not provide sufficient explanatory power to encompass the range and nature of impairments consistently found to be associated with the clinical diagnosis of autism.

The final set of beliefs are treatment-centered beliefs. These generally posit no unique deficit but hold that autism is best understood as a disorder for which special forms of education are crucially necessary. In *Autism,* Laura Schreibman devotes most of her explanatory energy to outlining an educational treatment method—behavior modification—that has met with the greatest success in helping autistic individuals to function more successfully. In chapter 6, "Specifics of Behavioral Treatment," Schreibman describes the behavioral excesses and deficits of autistic individuals. She goes on to consider the generalization of treatment effects.

Embedded in Schreibman's discussion of treatment methods is a deficit-centered claim for the unification of the syndrome of autism. Schreibman states that a substantial body of behavioral research has identified a particular pattern of attention wherein many autistic children, when presented with a learning situation requiring response to simultaneous multiple cues, characteristically respond to a very restricted number of the available cues. This pattern of attention has been labeled "stimulus overselectivity" (*Autism*, p. 111).

For Schreibman, stimulus overselectivity is the key deficit of autism—the deficit that behavioral modification can address and ameliorate. As Schreibman points out, most learning situations involve multiple cues; therefore, if autistic children always "overselect" some limited set of environmental information, autistic children will be impaired in most learning situations. For Schreibman, behavioral modification training is important because it works toward development of both temporal generalization—maintaining a behavioral pattern over time—and stimulus generalization—maintaining a response set to a stimulus across different situations.

Both Frith and Schreibman provide clear and careful summaries of the history and state of the field. Both make strong arguments for the nature of the deficit they envision to be the defining one for the syndrome of autism. Are these deficits—failure to achieve global coherence and failure to attend to multiple stimuli—one and the same?

Recently Margaret Bauman conducted analyses of whole-brain serial sections of the brains of seven autistic males. She found no anatomical or cellular deficits in the neocortex, but she did find too many cells, all of which were immature, in the limbic system tissue of all seven brains. If one of the limbic system's central functions is to create long-term memories based on the arousal salience of impinging environmental experience, then it may be that in autism, the yoked arousal and memory-forming capacities are impaired in ways that constrain an individual's ability to focus on multiple cues by limiting the functional integration of working memory. It may also be that fragmented working memory and limits to the formation of long-term memory have negative effects farther "downstream" in behavior, curtailing the creation and memorial establishment of all sorts of imaginative representations.

Both of these books deserve a place on the bookshelf of those working in the field. For those not working in the field, either would provide a good introduction to previous research and theory, with the caveat that each is centered on a specific but limited belief about the unity of deficit across individuals who can be identified as autistic.

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**Autism: Nature, Diagnosis, and Treatment,** *edited by Geraldine Dawson. New York, Guilford Press, 1989, 417 pp., $45.00.*

This book is an important contribution to autism research, bringing together the data and viewpoints of many of the prominent investigators in the field. The book is divided into two broad sections, the first on the nature of autism as seen from different perspectives and the second predominately on treatment issues. An excellent foreword is provided by Dr. Eric Schopler.

In section one, Perspectives on the Nature of Autism, five chapters review the various psychological perspectives on the essential nature of autism. These chapters focus on the social, cognitive, language, and attentional deficits in autism, exploring their possible roles in the genesis of this clinical syndrome and proposing different theories on the likely primary deficit. In general, this segment of the book emphasizes the primacy of disturbances in early social-affective development, proposing that other deficits arise as a consequence of these early developmental deficits. A particular strength of this segment is the thorough and evenhanded presentation of data followed by the author's analysis and views of the meaning of the data. This approach provides the reader with a thorough review of the existing data and avoids the bias of a theory-driven view of the literature.

A limitation of the general viewpoint represented in these chapters is the failure to consider the existence of early developmental deficits in nonverbal cognition. These early deficits are not easy to assess but are nonetheless present; their existence calls into question the primacy of the social-affective deficit. A second limitation is that the authors have not considered the possibility that all the deficits—social, language, and cognitive—could be dependent on a common neural substrate, i.e., the association cortex. This omission is apparent, for example, in their discussion of attention and arousal; the authors speculate on the adverse effect of attentional deficits on information processing but do not consider the obvious converse possibility that lack of comprehension of the meaning of an object or situation may affect attention.

The second part of section one presents several neurobiological perspectives that emphasize the primary role of subcortical mechanisms in the pathogenesis of this syndrome. Although the authors of these chapters emphasize the function of the nervous system in terms of neural circuits and specifically propose dysfunction within the cortical-limbic-reticular system, they emphasize a subcortical origin for the pathogenesis of the clinical deficits arising from the cortex. Absent from this section are chapters by Bauman and Kemper on neuropathological findings in autism and by Rumsey and Hamburger on neuropsychological findings. The last two chapters in this section cover the topics of neurotransmitter abnormalities in autism and genetic issues, respectively. The neurochemistry chapter by Volkmar and Anderson provides an excellent review of this area.

Section two provides chapters on diagnosis and various aspects of treatment, including methods for increasing language use and social interactions in autistic children and pharmacological treatments. The single chapter on diagnosis, by Waterhouse, Wing, and Fein, primarily underlines diagnostic difficulties and, indeed, makes a case for the absence of a definable syndrome. Although it is worthwhile to consider the inadequacies of diagnostic criteria for describing the syndromes of autism and the difficulties of clinicians in applying these criteria, the existence of autism as a recognizable syndrome is undeniable. In regard to the authors' comments on the inadequacies of all theories seeking to explain autism and hence to validate the clinical syndrome, it is worth remembering that the complexity of the structure and function of the nervous system is still far beyond our current understanding. We can expect those limitations to be reflected in our data and theories regarding all CNS disorders. Rather than expecting "the answer," we can expect a progressive shaping of theories about the pathogenesis of autism over time, reflecting gains in both our understanding of the deficits in autism and of the structure and function of the CNS. The adequacy of current data and theories should not be used as an index of the validity of the clinical syndrome. The coverage of diagnostic issues in this section suffers substantially from the absence of chapters covering the clinical syndrome as it is defined, the conceptual advances engendered in *DSM-III-R* criteria, diagnostic instruments that have made inroads into the standardization of diagnosis, and future directions in diagnosis research.

The treatment chapters provide a nice review of research issues and focuses for behavioral intervention. The chapter on pharmacological treatment provides a thorough review of the efficacy data on the various medications considered in autism.

In summary, this book is an excellent contribution to the research literature and a worthwhile purchase. It has a great many strengths and some limitations, primarily in the area of omissions. Some chapters will be of value to anyone dealing with autistic individuals, but others will primarily be of interest to those more involved with research and program development.

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## PSYCHOANALYSIS

**Nuances of Technique in Dynamic Psychotherapy,** *by Mardi J. Horowitz, M.D. Northvale, N.J., Jason Aronson, 1989, 268 pp., $27.50.*

This book is a collection of papers (published mainly in the 1970s) that Horowitz has "brought together for the first time because they describe a domain of concern for the individual style and capacities of the patient." Horowitz's description of this "domain" is brilliant and reveals a first-rate mind fully engaged in the enterprise—eclectic, shrewd, and artful.

The major contribution of this book is its integration of cognitive theory and contemporary psychoanalytic theory, an important development at the time these papers were written. Cognitive considerations inform Horowitz's conceptions of etiology as well as therapy, and he convincingly explains how new cognitive structures (broadly defined) are what produce change in psychotherapy. This means that the psychotherapist is a teacher and that how he or she teaches is as important as what is taught. Horowitz's emphasis is on how the patient learns, and that is only half the story. But the half of the story Horowitz tells is remarkable.

His book begins with the newest of these papers (published in 1986). Informed by his cognitive perspective, Horowitz defines eight levels of interpretation. This is his attempt to plumb the vertical dimension of depth psychology from the psychotherapist's perspective. Like many other ideas in the book, it makes eminent sense. These eight levels are then multiplied by three kinds of contexts: "current external situations," the "current therapy situation," and "past situations." Now the reader has 24 possible variations to think about, a cognitive map to locate the kind of interpretation he or she makes to the patient. Horowitz has begun the microdissection of the corpus of therapeutic communication that will permit microanalysis and the discussion of nuance. This kind of specification is characteristic of Horowitz's thinking, and he does it with a minimum of jargon.

Horowitz then turns to an important issue with an artful example. He seeks to demonstrate how learning takes place in psychotherapy and how that learning is crucial to working through. His example is a clinical vignette in which a patient composes a poem in a therapeutic hour. He gives us a microanalysis of the "cognitive maneuvers" of the patient and "the interrelationships among ideational structures, emotional responses and reactive control responses."

The next chapter, which one is tempted to call an essay, deals with therapeutic alliances with difficult patients. Written with Charles Marmar, M.D., it is a gem. The next three chapters deal with visual thought images in psychotherapy. These chapters allow Horowitz to discuss modes of thinking and feeling and not-thinking and not-feeling. The analysis is Proustian.

Horowitz then turns to trauma and traumatic stress disorder. He considers how character style influences the experience of trauma. He describes a traumatic episode and then imagines the patient, Harry, with three different personality styles: histrionic, compulsive, and narcissistic. The important issue is that the therapist not have one approach to traumatic stress disorder because different kinds of patients integrate "information" differently.

The last chapter is a tour de force—a description of a successful analysis emphasizing the cognitive changes that produced the result. Here most of all one feels that unfortunate psychoanalytic tradition which even in its clinical literature conceals the person of the analyst and thus deprives the reader and student of the opportunity to learn how the master teacher teaches the patient. The dust jacket of *Nuances* has the usual glowing endorsements. What is unusual is that the book fully deserves them.

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**Psychoanalysis and Motivation,** *by Joseph D. Lichtenberg. Hillsdale, N.J., Analytic Press, 1989, 422 pp., $39.95.*

In this masterful collection, synthesis, and reformulation of contemporary infant research, Joseph Lichtenberg seeks to extend our understanding of underlying motivational systems by using fresh psychoanalytic conceptualizations. Although not an infant observational researcher himself, Lichtenberg rests his work heavily on psychoanalysts who are, such as Mahler, Emde, Greenspan, Sander, and Stern, and integrates their findings with his own extensive clinical experience with adults. In contrast to the classical dual-drive theory, Lichtenberg offers five separate motivational systems and then demonstrates how they can orient the therapist in clinical work. A chapter contributed by June L. Hadley, M.D., suggests correlations between the five motivational systems and current advances in neurobiology.

Throughout the book, Lichtenberg attempts to demonstrate how the five motivational systems relate to each other and how the self acts as the center for initiating, organizing, and integrating motives. The five motivational systems are each based on clearly observable behavior that begins in the neonatal period.

The first motivational system discussed is the system based on the need for psychic regulation of physiological requirements involving hunger, thirst, elimination, tactile stimulation, equilibrium, thermal control, and sleep. When these requirements are coupled with the satisfactory participation of the caregiver, a quality of affective substrata that Lichtenberg calls a "selfobject" experience is established. Here he is applying Kohut's frame of reference and rejecting what he considers to be the blind drives of Freud. To Lichtenberg, psychological regulation of physiological requirements derives from the lived experience, which is optimal when the infant and the caregiver are well matched.

Lichtenberg's second motivational system is the attachment-affiliation system. Lichtenberg wants to shift from oral or nonoral preeminence to that of the five motivational systems: from infant as activator and the mother as responder to the interactional interplay of both; from instinctual behavior to mutual regulation; from attachment as behavior to the experience of pleasure in intimacy. Lichtenberg's concept of attachment is not based on what a baby does or the caregiver does but a mutual interregulation resulting from the activation of motivations and functions of both. In contrast to theories of early fusion or symbiotic merger, Lichtenberg believes that the infant must have a sense of self if there are five different motivational systems. His clinical experience causes him to doubt that even autistic children or withdrawn schizophrenic patients lose the differentiation of self from other. Lichtenberg believes that affective signals from the therapist play a major but often unrecognized role in facilitating or inhibiting patient behavior, just as is the case with the mother and her 1-year-old child. Lichtenberg reviews research on infant-father interaction in this area as well. It is not generally recognized that infants have clear-cut attachment reactions to fathers and often prefer fathers for some kinds of socializing and play despite their more vigorous and varied patterns.

In the third system, the exploratory-assertive motivational system, competence pleasure is an explicit demonstrable response. Lichtenberg believes that children and adults use the exploratory-assertive motivational system to solve conscious and unconscious intrapsychic and interpersonal problems in adaptation.

The fourth or aversive motivational system centers around antagonism/withdrawal (fight/flight) and is weak in early infancy. This system is largely dependent on the amount of success innate patterns have in serving as signals to evoke remedial patterns from caregivers. Older infants and toddlers add anger and fear but also need caregivers to induce or support aversive responses in danger situations. Lichtenberg includes learning to engage in and regulate controversy in this fourth system, a capacity that requires subjective awareness in the child of his or her own affective states and those of others. Some infants are powerless to restrict withdrawal responses to the signal level because caregivers are incapable of ameliorative responses that relieve distress and because stability and familiarity produce fear, anger, or sadness rather than relief. Similarly, some patients with severe personality disturbances seek the re-creation of aversive transference situations marked by fear, anger, and depression.

When Lichtenberg turns to the fifth system, the sensual-sexual motivational system, he finds few experimental studies and systematic observations. He believes that the role of erotogenic zones has been overstated and the role of caregiver activity understated.

Lichtenberg broadens the concept of "model scenes" he introduced in earlier work to describe important lived experiences of childhood that serve unconsciously to organize current experience as a means by which patients ascribe particular roles to themselves and to the analyst. The earlier the lived experience the more importance Lichtenberg attaches to how it is recorded, represented, maintained, or transformed. Crucial to the clinical application of Lichtenberg's theory is the therapist's appreciation of transitions in dominance from one motivational system to another. Affects are the best cues. Lichtenberg's discussion brings forward contemporary views of affects and acknowledges them as the givers of meaning to model scenes and the fuel for desired repetition.

Lichtenberg posits that the unconscious is occupied by his five motivational systems shaped by lived experience before and after the development of symbolic representation. To enter the state of mind of the analysand, the analyst must attend not only to the words and affects of ordinary free association but also to the behaviors, gestures, and affects that come from deeper layers. This allows the analyst to formulate model scenes after using the analyst's own affect-laden responses in addition to information gained from enactments in the intersubjective field of an ongoing analysis. Deficits in empathic responsiveness and their repair allow the innate "self-righting" of human beings to work in consonance with the capacity to reorganize symbolic representations. The result, in Lichtenberg's view, is analytic success.

The American Psychoanalytic Association honored this volume at its fall 1990 meeting. Readers of this journal from various vantage points within psychiatry would do well to study this book with care. Sampling it will provide the motivation.

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**A Safe Place: Laying the Groundwork of Psychotherapy,** *by Leston Havens, M.D. Cambridge, Mass., Harvard University Press, 1989, 158 pp., $22.50.*

Despite its brevity, simplicity, and lack of technical terms or concepts, this professional book can be read with satisfaction and benefit. What Dr. Havens says can be understood at many levels. For the beginner or interested nonprofessional, it is a most suitable entrance into the land of psychodynamic psychiatry and psychology. For the more experienced therapist, it reverberates with clinical experiences and allows the reader to understand patients from some new and different perspectives. One also gets the "feeling" of Dr. Havens—a sensitive observer, a wise professional, a thoughtful and reflective therapist, and a philosopher whose ideas are worthy of further study and reflection. A safe place is a haven where the distressed, disturbed, and diseased can be helped. I am certain that many see Dr. Havens as a source of safety, understanding, and healing. Thus, the term "a safe place" is perhaps a derivative of the original meaning of "asylum" as a place where one could be helped and comforted.

Dr. Havens uses his own clinical material to illustrate his points. These are human encounters and are based on careful observation and not on premature Procrustean formulations. The author is aware of the reader, himself, and the patient's dilemma. The safe place is the safe relationship, based on trust and confidence. Through the writing, which is scholarly without being technical or pretentious, one can imagine the type of therapeutic relationship Dr. Havens has with his patients. The book is suitable for the general reader, but the professional therapist can understand and apply what is so well stated to the clinical situation.

I do not agree with Dr. Havens when he speaks of Freud's "invention" of psychoanalysis—I would instead prefer talking about Freud's observations, discoveries, and attempts at understanding what he perceived. Freud did modify his hypotheses when they were at variance with additional clinical observations. But this is a relatively minor criticism of an otherwise excellent book.

Dr. Havens's discussion of the location of pathology is a stimulating new viewpoint. He writes, "Each of the psychiatric schools searches in a different place for its pathology and often restricts that search to one place" (p. 62). He goes on, "I believe too that some of the theoretical disagreements between opposing camps spring from their different attitudes. This is because the basic attitudes generate some of the material that forms the empirical foundations of the theories" (p. 64). Dr. Havens points out the necessity to question assumptions before accepting them as facts. His effective use of metaphor and analogy allows the reader to follow his discussions clearly and to decide on their utility.

In his section on depression, suicide, schizophrenia, and psychopathy, Dr. Havens again illustrates with brief clinical data the essences of his fundamental premises. He argues against simplistic labeling procedures and asserts that "suicide is the final common pathway of diverse circumstances . . . tightening around a single time and place, with the result, sign, symptom, trait, and act" (p. 79). The clinical illustrations in the chapter on schizophrenia again are clear and to the point.

Dr. Havens writes about the contributions of Sullivan in the context of present-day psychodynamic theories. This discussion can be read profitably by those unfamiliar with Sullivan's point of view. Dr. Havens notes that "psychotherapy is the name we give efforts to study and improve one's experience and view of things—one's subjectivity—with the help of another's subjectivity. We want to be as objective as possible about others, but we have to recognize that psychotherapy is shot through with the subjective and the historical" (p. 137). Dr. Havens shares his ideas and insights with the reader throughout the book. His last chapter, "The Future of Healing," is a statement very worthy of thought and is the blueprint he sees evolving for psychiatry and the other behavioral sciences.

This book is highly recommended.

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**The Psychotherapy of the Self,** *by Hyman L. Muslin and Eduardo R. Val. New York, Brunner/Mazel, 1987, 240 pp., $26.95.*

Muslin and Val have written a very concise and clear text on talking (or perhaps listening) therapy applicable to all types of patients. In the preface they state, "A major consideration has been our long-held wish to advance our view that psychotherapeutic treatment should be a planned effort based on carefully gathered data." This theme is carried out well and concretely illustrated in a series of ongoing case examples from the literature and the authors' own case material. This book deals with psychotherapeutic fundamentals well and carries the audience comfortably into material that is reasonably complex. The formulations of case material are based on Kohut's self psychology, but with little metapsychological discussion. The clearly written formulations allow the reader to translate them easily into other metapsychological frameworks or more basic psychological constructs.

The eight chapters of the book cover a brief but adequate overview of self psychology, psychotherapeutically oriented diagnosis, major individual therapy modalities in self psychology, the inner world of the psychotherapist, and an overview of the goals of the psychotherapies. In each chapter the reader is clearly shown how psychotherapy is going to be approached and formulated for different patients, and then the major approaches to treatment (supportive, psychoanalytic, and psychoanalysis) are described. The overview chapter emphasizes flexibility and illustrates examples of circumstances when it is appropriate to deviate from the predominant techniques of a given modality to techniques usually associated with another modality, such as the use of supportive techniques during crisis in a psychoanalytic treatment. Appropriate use of technique flexibility is not often well described in psychotherapy texts and will be particularly useful to beginning psychotherapists and trainees.

A possible problem with the book is that there has been no attempt to connect formulations or case material to schools of psychotherapy or major constructs in psychology other than self psychology. Although it could be argued that this would have diluted the crisp focus on psychotherapeutic technique, it could have been fairly easily done and would have been helpful to beginning students of psychotherapy. The exclusive focus is not a strong negative because the authors' use of simple, non-jargon-laden language makes comparison with other constructs an easy task for an instructor. Overall, this book is pleasant to read, will have something to offer most psychotherapists, and is very thorough.

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**Turning Points in Analytic Therapy: The Classic Cases,** *by Gerald Schoenewolf, Ph.D. Northvale, N.J., Jason Aronson, 1990, 231 pp., $30.00.*

Psychoanalysis has undergone many conceptual and technical changes, some would say advances, especially during the past two decades. Theoretically, the emphasis has shifted from a basic drive-centered psychodynamic hypothesis to an ego-oriented, structural viewpoint. Correspondingly, analysts' attitudes about therapy have relaxed considerably, and the image of the rigid, neutral analyst has become considerably blurred. Furthermore, the types of patients that therapists venture to engage in psychoanalytic treatment are supposedly quite different from those Freud and the early so-called classical analysts purportedly treated.

Psychoanalysts have reached a point in their evolution at which they can look back and examine the history of their development. They want to reevaluate certain basic dictums because, from a clinical therapeutic perspective, much of what they have been taught is not particularly useful.

Dr. Schoenewolf is another of many comparatively recent authors who penetrate the mystique that surrounded and preserved the ritualism and dogma of psychoanalytic principles and procedures. He believes that the turning points in psychoanalytic theory and practice have evolved from the treatment of specific patients. He begins with Breuer's patient, Anna O., and then moves to Freud's classic patients, Dora, Little Hans, the Rat Man, and the Wolf Man. (As dramatic as the last two appellations may be, I have always found them somewhat offensive.) These chapters are divided into two sections, the first being the case summary and the second dealing with other ways of formulating the clinical data that are more in harmony with the structural approach and object relations theory. In fact, Dr. Schoenewolf attempts to demonstrate how the patients of Breuer and Freud can be used to develop various theoretical constructs that are currently applied to the treatment process. To achieve this, he describes some of these patients as much more disturbed than the original analysts did. Many of the patients described seem now to have been suffering from severe characterological psychopathology and, in some instances, psychoses rather than classical psychoneuroses.

These chapters are interesting and informative, but the presentations do not furnish any additional perspectives for the experienced analyst. They are excellent summaries, however, for the inexperienced analyst or the general psychiatrist who has not extensively devoted himself or herself to the psychoanalytic literature. They are also handy in refreshing the memories of all analysts. The second section of reformulations also serves as a reminder and a compendium for those who wish to review the various critiques and discussions about these famous patients. Unfortunately, Lipton's well-known and provocative paper is not included in Schoenewolf's discussion of the Rat Man.

There is a naive and simplistic quality to some of the author's more sweeping generalizations. For example, he writes, "In Western society today women are allowed more freedom of expression than men and, in my opinion, are prone to acting our their hysterical rage through vehicles such as radical lesbianism or feminism." He also takes all of Ernest Jones's statements at face value. Jones related that Breuer fled from Anna O. when, suffering from pseudocyesis, she accused him of being the man who made her pregnant. According to Jones, Breuer went to Venice on a second honeymoon and impregnated his wife, who gave birth to a daughter who many years later committed suicide. It has been proven that there was no such daughter.

The remainder of the book is, in my opinion, much more valuable. Schoenewolf discusses the works of Ferenczi, Melanie Klein, Wilhelm Reich, Adler, Jung, and Binswanger. These authors, with the exception of Klein, have been comparatively neglected in the last several decades. Schoenewolf presents a lucid summary of their ideas and clinical experiences and then demonstrates how their thinking has shaped many of our current concepts and technical approaches. The reader can learn a good deal about these schools without having to search the literature laboriously.

This book is rewarding in that it provides a scholarly account of the development of many fundamental psychoanalytic principles. It broadens our historical perspective in that it focuses on how various "deviant" schools originated and how they, in turn, have been incorporated into our thinking without having been acknowledged.

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## SLEEPING AND EATING

**Brainstem Control of Wakefulness and Sleep,** *by Mircea Steriade and Robert W. McCarley. New York, Plenum, 433 pp., $85.00.*

Fortunately, two preeminent sleep biologists have answered the call to organize the mountain of new information about the brainstem neurobiology of sleep and wakefulness. The product is a clearly written and beautifully illustrated volume. Moreover, the data presented are absolutely current. A neuroanatomist with extensive expertise in reticular formation biology spontaneously remarked, "Great book!" on reading it, confirming my suspicion that a huge gap has been filled by this beautifully rendered volume.

After the introductory chapter, the authors review and carefully critique anterograde and retrograde anatomic tracing methodologies. The following two chapters begin to clarify the known neuroanatomy of the reticular formation and its connections to the thalamus and other brain regions. A neuroanatomical component is woven through the remaining text as well, however. A remarkable number of brainstem nuclei and many of their neuroanatomical connections have now been elucidated. In fact, each nucleus has its own abbreviation, and occasionally I was literally overwhelmed by the number of abbreviations in a given paragraph or sentence. An appendix of abbreviations would have helped circumvent this problem. Some critical emerging players that may be unfamiliar to the psychiatric readership are the pedunculopontine nucleus (PPT) and the laterodorsal tegmental nucleus (LDT), the two cholinergic brainstem reticular formation nuclei. The role of these nuclei in generating REM sleep and "uploading" the information processing capacity of the thalamus are major themes.

Next, electrophysiological evidence, including intracellular recordings, is presented to clarify the functional relationships among brainstem structures. Ionic conductance and other aspects of "pacemaker" physiology unique to several brainstem structures may again prove informative to the psychiatric readership. Pontogeniculooccipital waves, which are associated with REM sleep and may, in fact, be the physiological manifestation of this state, receive much attention, including an entire chapter. The authors also defend the position that the intracellular physiological hallmark of REM in relevant reticular formation nuclei is tonic depolarization.

The authors are not entirely successful in "wrapping up" this enormous amount of information in their concluding chapters. Mathematical models are often problematic when translated to the human animal, and the clinical section is more notable for an absence of speculation than new information.

This dense tour de force in modern neurobiology is obviously of most interest to neuropsychiatrists and those interested in sleep. It is also obvious that from this juncture forward, it will take a more powerful effort in psychiatry to keep in step with the march of neuroscience.

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**Why We Sleep: The Functions of Sleep in Humans and Other Mammals,** *by James Horne. New York, Oxford University Press, 1988, 314 pp., $49.95.*

Despite a burgeoning interest in sleep, sleep disorders, and sleep alterations in psychopathological conditions over the past 20 years, progress has been hampered by our ignorance regarding the basic functions of sleep. James Horne has addressed this ambitious topic in his scholarly book, which is the culmination and refinement of his earlier writings. The result is not only a critical and comprehensive review of the literature regarding sleep effects on cerebral and physical function but also presentations of several new—and controversial—ideas.

Horne's clarity of purpose and style are evident in the introduction, where he lays out his arguments and goals. This helps to focus the reader for subsequent chapters. In the first two chapters, he reviews the literature on animal and human sleep deprivation experiments, providing an interesting historical overview as well as a critical review of possible confounds with these experiments. In particular, Horne carefully discusses results of various performance measures that show sleep deprivation effects and factors with a possible influence on sleep deprivation effects. Horne notes that there are few data regarding creative and "divergent" cognitive processes in humans subjected to sleep deprivation. He also begins to develop his notions of "core" and "optimal" sleep and relates these to some of the more unexpected findings in sleep deprivation studies.

Horne then delves into the restitutive effects of sleep for both body and brain, concluding that sleep provides clear benefits for the brain but little restitution for the body. In challenging our usual assumptions about sleep and physical recuperation, one might argue that Horne focuses too narrowly on protein metabolism as an indicator of body restitution, although there are much fewer data (and certainly fewer recent data) available regarding this topic.

In the chapter "Core and Optional Sleep," Horne presents the major tenets of his argument. Specifically, he argues that sleep consists of a core component (i.e., necessary for cerebral restitution), and an optional portion (i.e., behaviorally motivated, which essentially serves as an occupier of time). Such a distinction, he argues, is more important than the traditional examination of REM and non-REM sleep distinctions. In this cornerstone chapter, Horne again challenges many commonly held beliefs regarding sleep requirements. He points to the lack of observable effects when sleep is reduced in length and to the "recovery" of only slow-wave sleep and a smaller portion of REM sleep following sleep deprivation.

Horne then embarks on a review of sleep in mammals other than man, again providing a comprehensive review of the available literature. He argues that sleep may have different functions in different animals rather than serving a single function in all. Although there are gaps in our knowledge regarding sleep in different species, Horne presents compelling arguments regarding the evolution and adaptation of sleep.

The final major chapter of the book is dedicated to an examination of REM sleep and dreaming. Once again, the author is not only scholarly in his review of the literature (particularly on dream function) but provocative as well. For instance, in his discussion of thermoregulation in sleep, Horne rejects the traditional notion of poikilothermy during REM sleep. He also asserts that REM sleep may be a "neotenous" function, involving fetal-like mechanisms rather than phylogenetically primitive ones. With regard to dreaming, he makes no definitive conclusions but presents available theories in an informed and evenhanded manner.

The strengths of Horne's work include its clear and informal writing style, apt analogies, and clear illustrations. Also to be commended are its comprehensiveness, originality, and critical view of the literature, which points to deficiencies in our knowledge base. Even more important, several of Horne's theories provide a basis for future empirical research.

Relative to these strong points, minor weaknesses also exist, including admittedly speculative or teleological arguments in the discussions of sleep in other mammals and (to a lesser extent) physical effects of sleep and sleep deprivation. Horne occasionally extrapolates in areas that are more central to his arguments, such as the presumed absence of long-term effects of decreases in optional sleep. It might also be argued that he downplays physiological sleepiness itself as an important consequence of sleep loss. Finally, although Horne clearly distinguishes between basic sleep research and the emerging field of sleep disorders medicine, the further use of clinical examples from sleep disorders may in fact have strengthened his arguments regarding the functions of sleep.

Overall, the strengths of this work far outweigh its weaknesses. It is highly recommended to those with a scientific or even a more casual interest in sleep and its disorders. This would certainly include psychiatrists, who are daily confronted with sleep problems in their patients. Horne offers creative and intelligent insights into one of the more puzzling aspects of human and mammalian brain function.

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**Anorexia Nervosa and Other Dyscontrol Syndromes,** *by E.L. Edelstein. New York, Springer-Verlag, 1989, 114 pp., $35.00 (paper).*

Unlike other contemporary publications on eating disorders, which tend to collect the expertise of several investigators, this text is written in one piece under a theme. Dr. Edelstein considers the current classification of eating disorders too narrow for the human experience. In this book he takes the interesting position that viewing anorexia nervosa and bulimia along a continuum of dyscontrol syndromes with obesity, drug abuse, activity addiction, and gambling might have heuristic and explanatory appeal. The psychopathology and pathophysiology of each of these syndromes is conceptualized along a line of drive and self-control and is thought to represent various coping measures to attain independence and autonomy from internal and external pressures.

The control and compulsive-dependent elements in anorexia nervosa have received renewed attention with the discovery of opioid receptors, but, as Edelstein points out, such elements have been recognized for a long time. For instance, the German term *Pubertätsmagersucht* ("addiction to thinness in puberty") refers to these aspects in the illness process.

The book discusses primarily the syndrome of anorexia nervosa. Of its 11 chapters, the first five discuss the history of the illness, including the feminine aspects and diagnostic criteria; habitual fasting and its relationship to religious practice; the regulation of feeding; studies on the body image; and the biological aspects of anorexia nervosa. Bulimia and obesity are briefly touched on in chapters six and seven.

The overall description is lively and instructive and, not surprisingly, guided by the author's research interests. The volume is well-equipped with references. Nevertheless, throughout the book appear such statements as, "The influence of the father as a major contributing factor in anorexia nervosa has not been fully investigated," for which the reader wants access to a source or data.

Chapter eight returns to the theme of dyscontrol syndromes. A 3-page table compares the motivational, emotional, and psychosocial elements of the disturbed behavior in anorexia nervosa, obesity, and drug dependence, collating astute observational and factual material, although some attributions would be considered tentative at most. Here, regrettably, the author misses the opportunity to examine his excellent hypothesis further, given the evidence and data in the literature.

The last three chapters integrate the author's own clinical and therapeutic approach with other publications. Among the many valuable comments and suggestions, I liked one in particular: "From birth on, the infant is delivered into the climate of the mother's affect."

This is a comprehensive book, and I recommend it as a good starting point to students. Both the biology and psychodynamics of clinical issues are treated thoughtfully; the book refers to current research and comments on treatment. The material is diverse enough to capture the interest of novices to the field.

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*Reprints of Book Forum reviews are not available.*

# Letters to the Editor

## Obsessions and Compulsions Associated With Cocaine Abuse

Sir: For years clinicians have observed an association between amphetamine use and the emergence of obsessive thoughts and compulsive behavior (1). Reports have documented cocaine-induced exacerbation of characteristic obsessions and compulsions in individuals with current primary diagnoses of obsessive-compulsive disorder (2, 3). In addition, diagnosis of obsessive-compulsive symptoms in children receiving *d*-amphetamine or methylphenidate for the treatment of attention deficit disorder has been described (4). We report a cocaine-abusing adult with a family history of obsessive-compulsive disorder and a childhood history of attention deficit disorder who manifested obsessive thoughts and compulsive behavior only during intoxication with cocaine. To our knowledge, this is the first report of the development of obsessions and compulsions upon exposure to cocaine in an individual without a current diagnosis of attention deficit disorder, obsessive-compulsive disorder, or other primary psychiatric disorder.

> Mr. A was a 34-year-old man who had abused cocaine for 10 years. Initially, he took 7 g/week by the nasal route; he then switched to freebase use and smoked up to 2 oz (56 g) per week in binges of 24–36 hours twice a week. After 5 years of use, coinciding with the switch to freebase smoking, the patient became obsessed with the desire to "see what the insides of things were like" and repeatedly dismantled his computer and, on occasion, put it back together. These thoughts and compulsions occurred only during intoxication with cocaine. Although he realized the irrational nature of his behavior, the patient felt compelled to perform this activity when using cocaine. He denied all forms of obsessional thinking and compulsive behavior outside the context of cocaine use.
>
> Mr. A did not meet criteria for *DSM-III-R* diagnoses other than cocaine dependence. Retrospectively, he met the *DSM-III-R* criteria for attention deficit hyperactivity disorder. He had never received treatment with stimulants or other agents. His cocaine use began at age 24, about 7 years after the symptoms of attention deficit hyperactivity disorder had resolved completely. The family history was notable for two brothers, among four siblings, who had obsessive-compulsive disorder manifested as disabling checking and hand washing, respectively.

This case suggests that identifying individuals with a past history or a family history of obsessive-compulsive disorder or attention deficit disorder might unmask a latent neurobiological vulnerability leading to the emergence of obsessive-compulsive symptoms only during intoxication with cocaine. Cocaine and other psychostimulants are known to have facilitative effects on dopamine and serotonin neurotransmission. This report is consistent with recent findings suggesting that dopaminergic as well as serotonergic dysregulation may contribute to the pathophysiology of some types of obsessive-compulsive phenomena (5).

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CHRISTOPHER J. MCDOUGLE
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## Routine Tests of Drugs

Sir: It has come to my attention that the "routine" blood tests done for clozapine, which were designed to protect the manufacturer from malpractice claims, did not include liver function tests. I recently saw a patient with very elevated liver function test results who was taking clozapine, and to my dismay I discovered that no pre-clozapine baseline values had been established. I believe that this is yet more proof that bureaucratic intervention, rules, regulations, and managed care are no substitute for sound clinical judgment, and I am very pleased to learn that the courts have now given back to psychiatrists the power to order and monitor the laboratory tests of their own patients.

Unfortunately, the reasoning of the courts was not based on clinical considerations but on antitrust considerations, and we must therefore remain vigilant against further erosions of autonomy based on economic rather than medical and humanistic values.

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## Weight Loss and Depression

Sir: Two recent clinical experiences raised for me the question of the relation between weight-reduction diets and serious depression. I report my experiences with two outpatients I had previously successfully treated for depressive disorders. Each had been in remission for substantially more than a year, but each had a recurrence 6–8 weeks after beginning a weight-loss diet. Neither was depressed at the time she undertook the diet.

> Ms. A was a 49-year-old woman whom I had first treated for depression when she was 39. Twelve years earlier, she had been treated for this problem elsewhere with psychotherapy and an antidepressant. Her diagnosis was major

depression, recurrent. I treated her with desipramine and psychotherapy, and she responded well. After termination of her treatment, she was euthymic for 7 years, until she had a recurrence during the sixth week of a commercial weight-reduction diet. This program involved a low-calorie diet and a food supplement but no appetite suppressants. Her weight had decreased by 20 lb, from 174 to 154 lb. She responded well to a therapeutic level of the antidepressant.

Ms. B was a 31-year-old woman who had had five previous episodes of depression, treated elsewhere, dating back to age 22. Her diagnosis was major depression, recurrent. When she was 29 she experienced a depression that I treated with psychotherapy and perphenazine, which had previously been successful for her. Upon termination of this treatment, she remained euthymic for 20 months. Then she had a recurrence after 8 weeks of a self-structured, reduced-calorie diet in which she used no appetite suppressants. She had sustained a 27-lb weight loss, from 167 to 140 lb. Her depression responded well to perphenazine and psychotherapy.

Cumulatively, studies of mood disorders following weight-reduction dieting have yielded conflicting and inconclusive results; some patients improve affectively and others become depressed. Smoller et al. (1), in an extensive review of the literature, found that the apparent conflict among studies resulted from the ways in which mood changes were measured. Wing et al. (2) proposed that the more recent studies failed to find serious mood disorders because persons with preexisting psychopathology were excluded from these studies. I could find no references in the literature published since 1986 that addressed the impact of such diets on previously depressed patients.

While persons without previous depression may not be at risk as a result of a weight-reduction regimen, these cases indicate that persons with such a history are at risk of recurrence, particularly with a weight loss of 20 lb or more (1). It is possible that some psychological process, such as a concern for low self-esteem, may have been a precursor of the depression. Or the connection between the depression and the diet may have been coincidental, so that to conclude that dieting was the cause of the depression is unwarranted. Nonetheless, these cases suggest that previously depressed patients may be at risk and should be monitored carefully if they embark on a weight-reduction diet.

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## Cognitive Dysfunction Associated With Fluoxetine

SIR: Cognitive impairment associated with tricyclic antidepressants has been attributed to sedative and/or anticholinergic effects (1). Accordingly, fluoxetine, with its low propensities for both, may be relatively free of adverse cognitive effects. Even so, cognitive dysfunction has been linked with fluoxetine (personal communication from Eli Lilly and Company), and the response of a patient I recently treated illustrates this.

Ms. A was a 60-year-old Caucasian woman whose recurrent major depressive disorder had responded to fluoxetine, 20 mg/day, prescribed along with conjugated estrogens, progesterone, and L-thyroxine, 0.15 mg/day (for chronic hypothyroidism). She presented with a 9-month history of difficulties with memory and learning unaccompanied by depression, sedation, anticholinergic signs, sleep disturbance, or current or prior use of licit or illicit substances with amnesic effects. Examples of her difficulties included forgetting that she had made bank deposits, leaving out key ingredients in recipes, failing to learn piano pieces (which caused her to retire as a piano teacher), and inability to learn a foreign language in preparation for a trip.

Although euthymic, alert, and oriented to person, place, and time on mental status examination, Ms. A, a college graduate, was able to recall only one of eight associative word pairs (four of eight is normal), only two of three items after 5 minutes, and only one president. Her fund of general information was poor, and she made several errors during serial subtraction of sevens. Her interpretation of proverbs was concrete and personalized. Her thyroid functions were normal, as were the results of both medical and neurological evaluations.

Fluoxetine was discontinued at Ms. A's first visit, while her other medications remained constant. Over the ensuing week, she reported that her mind seemed clearer and her memory better. Then, since she reported recurrent depressive symptoms, she was started on a regimen of nortriptyline, 40 mg h.s. (which produced a 12-hour steady-state plasma level of 137 ng/ml) and responded well. Eighteen days after discontinuing fluoxetine, she returned for a follow-up visit, during which her cognitive functioning was significantly improved: she was now able to remember five associative learning pairs, remember three of three items after 5 minutes, perform serial subtraction of sevens without error, and recall five past presidents. When her nortriptyline dose was reduced to 30 mg h.s. because of weight gain, she became more depressed but experienced no cognitive dysfunction. Her dose of nortriptyline was then increased to 40 mg h.s. (producing a 12-hour steady-state plasma level of 97 ng/ml), and her depressive symptoms resolved. Over the ensuing 3 months, she reported no memory difficulties, and after successfully resuming her household duties and her career as a piano teacher and learning the foreign language she had been unable to master while taking fluoxetine, she departed on her trip.

Ms. A's reversible cognitive dysfunction appeared to be related to fluoxetine treatment. Although depression has been associated with cognitive dysfunction, Ms. A was euthymic at the time of her first mental status examination and did not develop cognitive difficulties when she became more depressed upon discontinuing fluoxetine or upon reducing her dose of nortriptyline. Moreover, she was not sedated, sleep deprived, or hypothyroid, nor did she have a fluoxetine-induced syndrome of inappropriate secretion of antidiuretic hormone or anticholinergic symptoms or signs. Although diminished performance on a coding task has been associated with fluoxetine in one study (2), two others (3, 4) have reported unchanged or improved cognitive function during fluoxetine treatment. The mechanism by which fluoxetine may impair short-term memory or learning in some patients awaits further investigation.

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## Fluoxetine and Bleeding in Obsessive-Compulsive Disorder

Sir: Fluoxetine is a bicyclic antidepressant and a selective blocker of serotonin (5-HT) reuptake. Adverse vascular effects such as bruises, metrorrhagia, cerebrovascular accidents, hemoptysis, melena, hematemesis, hematuria, and vaginal bleeding after drug withdrawal have been sporadically reported (Dista Products Company, *Fluoxetine Hydrochloride, Adverse Reactions,* 1989).

We would like to report eight cases of bleeding in patients suffering from obsessive-compulsive disorder. None of these patients had ever noticed any bleeding episodes before they took fluoxetine.

The patients' ages ranged from 16 to 75 years, with a mean of 35.1 years. One patient was taking fluoxetine at a dose of 20 mg/day, one patient was taking 40 mg/day, and six patients were taking 80 mg/day. The duration of treatment ranged from 21 days to 1 year, with a mean of 150 days.

There was one report of melena, the cause of which was undetermined because the patient refused to be tested. There were four reports of rectal bleeding, three caused by internal hemorrhoids and one due to unknown factors, all confirmed by rectosigmoidoscopy. One patient reported scattered bruises on arms and legs and had an elevated level of liver enzymes. Another patient suffered from mild bilateral epistaxis; rhinoscopy showed mucosal vascular dilation. The following case may help to illustrate this report.

> Ms. A, a 75-year-old woman, had a history of concomitant emphysema, arteriosclerotic heart disease, angina, and colitis. She was placed on a regimen of fluoxetine, 20 mg/day, for a month. Then the dose was raised to 40 mg/day, and she took this dose for 2 months, until she had to be hospitalized because of constant generalized abdominal pain of sudden onset. The pathology report indicated a segment of the small bowel with moderate acute ulcerating inflammation and vascular dilation, recent hemorrhages, and submucosal edema consistent with vascular compromise.

Upon discontinuation of fluoxetine, no further episodes of bleeding were reported by any of these eight patients.

Serotonin is associated with the regulation of vessel constriction and dilation, notably that of mucosal vessels (1). Because large doses of fluoxetine may cause hyperserotonemia (2) in a defective vascular bed, as seen in our patients, an increase in 5-HT may serve as a mediator to precipitate the bleeding episode. When large doses of fluoxetine are prescribed for the treatment of obsessive-compulsive disorder, potentially significant bleeding problems in some patients, particularly those who have predisposing conditions, should be considered.

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## Fluoxetine and Reactivation of the Herpes Simplex Virus

Sir: We report three cases of reactivated herpes simplex virus infection associated with fluoxetine treatment.

> Ms. A was a 43-year-old white woman with recurrent major depression and a history of genital herpes, quiescent for more than a year. Within 1 month of her beginning to take fluoxetine, 20 mg/day, the herpes became reactivated. Although her depression responded well, the patient believed that the exacerbation of herpes was related to fluoxetine. Fluoxetine was replaced with desipramine, and there was partial relapse of the patient into depression but remission of the herpes. After 18 months on the desipramine regimen, Ms. A requested retreatment with fluoxetine. At 20 mg/day there was no improvement in her depression, so the dose was increased to 40 mg/day, and outbreaks of herpes began within 1 month. Because her depressive symptoms improved markedly with the dose of 40 mg/day, she elected to continue fluoxetine and to control the herpes with oral acyclovir. She continues to experience the tingling of an imminent outbreak of herpes monthly. When the tingling begins, one to two doses of acyclovir prevent vesicular eruptions. After 8 months of fluoxetine treatment, major depression has remitted.
>
> Ms. B was a 64-year-old white woman who presented with major depression and a remote history of labial herpes simplex. She was started on a regimen of fluoxetine, 20 mg/day. Approximately 2 weeks later, she developed vesicles on her lower lip that were typical of those she had had in the past. Her regular physician diagnosed herpes simplex. The patient discontinued fluoxetine and the lesions healed. Two weeks later she restarted fluoxetine, which she now has been taking for 2 months. There have been no further herpes outbreaks and her depression is well controlled.
>
> Mr. C was a 42-year-old white man who was given fluoxetine, 20 mg/day, for recurrent major depression. He also had recurrent genital herpes involving the skin on one side of his genitals. After beginning fluoxetine, the frequency of herpes outbreaks remained the same, but the pattern changed to involve both sides of his genitals. His depression resolved with fluoxetine, and he continues to take it despite the increase in herpetic lesions.

Recurrences of herpes simplex are thought to be related to lapses in cell-mediated immunity. After primary infection the virus lies dormant in sensory ganglia, and under various circumstances the virus is released and travels back to the previously involved sites, where vesiculation occurs. The triggers for release of the virus from sensory ganglia include sunlight, fever, trauma, menstruation, and emotional upset (1). None of the patients in this report was able to recall any increase in life stress. All were depressed but improving at the time of outbreak. In the first patient, recurrences of herpes while she was taking fluoxetine seemed associated with ovarian cycling.

To our knowledge, there are no previous reports of herpes reactivation associated with fluoxetine. Correspondence with the manufacturer indicated that there had been 10 cases of herpes simplex and eight cases of herpes zoster associated with fluoxetine since the medication was first marketed (personal communication, Eli Lilly and Company, May 1990).

The chronologic associations reported here suggest that there may be a relation between the use of fluoxetine and reactivation of the herpes virus.

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## Fluoxetine Treatment of Voyeurism

SIR: We read with interest the letter "Fluoxetine Treatment of Exhibitionism" by Michael D. Bianchi, M.D. (1). We would like to share our recent experience with fluoxetine in the treatment of voyeurism. Voyeurism is defined by *DSM-III-R* as a disorder that consists of recurrent, intense sexual urges and sexually arousing fantasies which involve the act of observing an unsuspecting person.

Mr. A, a 30-year-old white man, presented with a history of voyeurism that had lasted for the past 16 years. He would go to busy public places looking for a young woman not wearing a bra and follow her for as long as he could. Similarly, he would place a running video camera on the beach and focus on specific areas of a woman's anatomy. At work, he would climb into the ceiling and peer though the ventilation ducts into the women's bathroom.

Beginning about 6 months earlier, when his voyeuristic urges became ego dystonic, Mr. A worried that he might lose his job if he were ever caught. He had tried to rid himself of this behavior on his own but had been unsuccessful. He would find himself spending several hours a day in the situations just described, despite his attempts to resist.

Because of the similarity between obsessive-compulsive disorder and Mr. A's intrusive urges and compulsive voyeurism, he was given fluoxetine, 20 mg/day. The dose was quickly raised to 40 mg/day, and he was kept on this regimen for 1 month without improvement. The dose of medication was then raised to 60 mg/day. He started to feel some reduction in symptoms, and there was moderate reduction in the second month. By the third month, Mr. A was totally free of his intrusive urges and compulsive voyeurism. When he goes out to busy places like the grocery store, he is able to return immediately and spend the extra free time doing other things. He reports that the medication has helped him.

In this case, the patient responded to fluoxetine, which is reported to be effective for the treatment of obsessive-compulsive disorder (2). Recent reports suggest that other sexual disorders, such as exhibitionism (1), may be improved by fluoxetine. This suggests some similarities between paraphilias and obsessive-compulsive disorder. Ours is a single case report, but further study in this largely neglected area should be done.

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## Natural Histories of Anorexia Nervosa and Bulimia Nervosa

SIR: We have noted work by Kassett et al. (1) and Burket and Rand (2) regarding the onset of symptoms in the eating disorders anorexia nervosa and bulimia nervosa. We wish to present work of our own that supports the notion that the natural histories of anorexia nervosa and bulimia nervosa are highly variable.

We examined the charts of 64 patients with current bulimia nervosa who had histories of anorexia nervosa and 16 patients diagnosed as presently suffering from anorexia nervosa and bulimia nervosa together. Information regarding onset of anorexia and bulimia symptoms was abstracted by a research assistant who was blind to the hypotheses of the study and then reviewed by one of us (D.B.W.).

Of the 64 patients with current bulimia nervosa and a history of anorexia nervosa, 43.8% (N=28) showed clear onset of bulimia before the onset of anorexia, with later recovery from anorexia symptoms but persistence of bulimia. Nineteen (29.7%) of the 64 patients showed roughly contemporaneous (within 1 year) onset of anorexia and bulimia symptoms. These patients had recovered from anorexia by the time of assessment. Fifteen (23.4%) of the 64 patients showed clear onset of anorexia symptoms first, with the later development of bulimia and recovery from the anorexia symptoms.

The 16 patients with anorexia nervosa and bulimia nervosa together showed a similar pattern: 43.8% (N=7) had bulimia first, 25.0% (N=4) had the two disorders contemporaneously, and 25.0% (N=4) had anorexia first. Thus, the pattern did not differ significantly between the two groups of patients ($\chi^2$= 0.44, df=3, n.s.). Finally, 76.6% (N=49) of the group with current bulimia nervosa and a history of anorexia nervosa could be identified as having suffered from bulimia and anorexia contemporaneously at some time in the past.

We believe that these data challenge the often-held belief that bulimia is a complication of anorexia when the two have occurred in the same individual. We also note that these results should give pause to those who wish to view anorexia and bulimia together as a special diagnostic category or as having a worse prognosis (3): bulimia with a history of anorexia is usually diagnosed as bulimia alone, and it appears that most of these patients could have been diagnosed as having anorexia and bulimia together at some time in the past. While these data cannot help resolve the question of whether anorexia nervosa and bulimia nervosa are etiologically distinct entities, it may be important to clarify whether there is a subgroup of bulimia patients who have a worse prognosis by virtue of also experiencing symptoms of anorexia.

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WENDI ROCKERT, B.A.
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*Toronto, Ont., Canada*

## Cost of Psychiatric Illness Versus Cost of Psychiatric Research

Sɪʀ: In reviewing the various aspects of the cost of psychiatric illness, the comparative cost of psychiatric research is an important factor to consider. Specifically, the pertinent questions are the following: What is the estimated cost to society of psychiatric illness? How does the cost compare to the cost of other illnesses to society? What is the percentage of total research money spent on psychiatric illness versus the percentage of research money spent on these other illnesses? If there is a discrepancy in the percentages, what can be done to correct it?

There is substantial evidence that in the United States the overall cost of mental disorders, including schizophrenia, in both personal and social terms (i.e., health costs and lost productivity) is close to, if not now in excess of, $200 billion per year (1). This figure is thought to be comparable to the overall costs per year of cardiovascular disease and cancer. On the other hand, mental health research has never received a level of support commensurate with the heavy cost of the disorders it has investigated or comparable to the research support for cardiovascular disease and cancer, the overall costs of which, as noted, have been shown to be similar.

Thus, we are confronted with two types of discrepancies—if not discrimination. The first is the discrepancy between the cost of psychiatric illness per se and the money society spends for its management as compared to the money society spends on other chronic illnesses of similar impact. The second discrepancy revolves around the money society spends for research in psychiatry versus the money society spends for research on the cause and treatment of similar conditions. What is needed now is a systematic effort by psychiatric researchers to document and present to the public and their representatives, especially the decision makers, these discrepant findings in full detail and to discuss their implications and repercussions. Already a first step toward such an effort has been undertaken by an international group, and its results were published in 1986 (2).

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## Outcome Studies' Effects on Clinical Practice

Sɪʀ: At our residents' journal club, which I supervise, the article under discussion dealt with a comparison of pharmacology and psychotherapies in the treatment of depression. The faculty discussant asked whether the results would in any way influence the residents' clinical practice. Several answered in the negative, agreeing that each case has to be viewed individually and that one needs to rely on one's own experience.

A resident described the satisfaction of helping a depressed patient by using a particular kind of therapy that had not been included in the article. The discussant asked the residents whether negative results from a trial of such a therapy would influence their behavior. Again, there seemed to be little inclination to allow the results of systematic studies to influence clinical practice. Possibly this reflects a healthy skepticism about research, but more likely it suggests that outcome studies are not measuring the most salient variable: how the treatment affects the therapist. Did he or she enjoy the treatment? Was it challenging and self-actualizing? Perhaps we need to develop a scale for this and use it in future comparative studies of treatment modalities.

I hypothesize that such studies would find that a treatment's acceptance by the profession may be more highly correlated with its therapist-enhancing effects than with its clinical efficacy.

DANIEL J. LUCHINS, M.D.
*Chicago, Ill.*

## Déjà Vu and Synesthesia

Sɪʀ: In regard to the interesting article on déjà vu phenomena by Herman N. Sno, M.D., and Don H. Linszen, M.D. (1), I would like to call readers' attention to an additional hypothesis that I proposed in 1966 in a presentation to the American Psychiatric Association, "Déjà Vu Phenomena—Observations and a Theory"(2), and more recently in a book, *Multiple Realities in Clinical Practice* (3). The central idea in this hypothesis connects déjà vu phenomena to synesthesia.

> As a schematic introduction to the idea, imagine that a particular wave pattern on an oscilloscope represents visual, auditory, or tactile stimuli. A responding organism or electronic scanning machine is then asked if this is a familiar *visual* pattern. Obviously, if the response is to the *pattern,* whatever the sensory modality involved, the likelihood that it will be familiar is much increased. That is, a déjà vu or related sensation will be aroused if the pattern of the visual stimulation evokes a corresponding echo in *any* other sensory compartment, be it auditory, tactile, or the like. In other words, if a certain pattern of stimulation, let us say a visual pattern, occurs at a time when the sensory compartments are particularly interwoven, particularly blended, the chances that the pattern will arouse a feeling of familiarity are multiplied. (3, p. 46).

It is interesting to note that some neurological disorders involving the temporal lobe are associated with many déjà vu and synesthetic experiences. This double association supports the proposed hypothesis of the déjà vu mechanism.

Dr. Sno and Dr. Linszen stated that "up to now, holography has not been used as a memory model to explain the déjà vu experience." Although this is true of their particular and interesting way of using holography as a memory model, I have used holography in a different way in my discussion of déjà vu phenomena. I have referred to the work of Longuet-Higgins, who has used the mathematics of holography (each point in space has some information about all other points in space) and transposed it to the temporal domain. Briefly, he has constructed a model of the CNS as a temporal hologram, a "holophone," in which each point in time has information about all other points in time.

> He postulates cells in the cerebral cortex that respond specifically to particular rhythms, just as there are known to be cells that fire only in the presence of specific visible features and arrays of cells that when briefly stimulated discharge rhythmically for some time afterward. He asks whether their thresholds for rhythmic firing can be altered by rhythmic stimulation. (3, p. 167)

Longuet-Higgins's work is relevant to my ideas about déjà vu phenomena. The similarity of rhythmic patterns can be considered the equivalent of an oscilloscope pattern that represents visual, auditory, or tactile stimuli, or their representation in a synesthetic mode. I would like to compliment Dr. Sno and Dr. Linszen for their work in an area in which, as is generally true of memory research in our current state of knowledge, psychodynamic and biological ideas meet.

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JOHN S. KAFKA, M.D.
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### Dr. Sno and Dr. Linszen Reply

SIR: We would like to thank Dr. Kafka for his thoughtful comments. Despite meticulous examination of the literature, we were unaware of his interesting hypothesis on the déjà vu experience. His letter demonstrates that for authors, publishing a paper serves not only to convey what they have learned but to acquire more knowledge as well. We are delighted to learn that Dr. Kafka acknowledges and once more emphasizes the importance of integration of biological and psychodynamic ideas.

HERMAN N. SNO, M.D.
DON H. LINSZEN, M.D.
*Amsterdam, The Netherlands*

### Childhood Experience and Borderline Personality Disorder

SIR: In reference to the article "Perceptions of Parental Bonding in Borderline Patients" by Joel Paris, M.D., and Hallie Frank, Ph.D. (1) and the subsequent letter from James L. Knoll III, M.D. (2), I would heartily support Dr. Knoll's hypothesis that some patients having a borderline personality organization (particularly those with narcissistic personality structure) are more likely to have been overprotected and overgratified during infancy, only later to be traumatized when the mother was unable or unwilling to continue to meet the demands of the often "exceptional" child. In my experience (3), this leaves the child with the subjective experience of being deprived rather than, necessarily, with the absolute developmental privation to which many authors have subscribed. Some therapists have based their therapy and interventions on the fantasy of presumed empathic restoration and affective attunement to deal with such early losses, without full appreciation of the differences in outcome between deprivation as an experience and the objective state of being without, which may or may not be experienced as a loss or even noted as exceptional. In my opinion, it is more likely the borderline patients in this latter situation who suffer most from identity problems, immature defenses, and unstable relationships but often do so without memory of, or even comment on, their lack of nurturing.

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DOUGLAS H. FRAYN, M.D., F.R.C.P.(C)
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### Dr. Paris and Dr. Zweig-Frank Reply

SIR: We agree with Dr. Frayn that the effects of childhood experience on borderline personality are complex, but we cannot accept the epistemological bases of his argument. As we acknowledged in our article, there are problems in asking adult patients to remember accurately their lives with their parents. However, we think that our instrument (1), which asked for overall ratings of neglect and overprotection in the first 16 years of life, is a reasonable way to assess these experiences systematically. In contrast, we cannot see how Dr. Frayn can validate his statements about infancy, which patients cannot recollect. We presume his views are based on theories that attribute severe character pathology to the earliest periods of development. We know of no empirical support for such theories, and it is not even clear if there is any way of testing them.

It is of interest, however, that in a larger sample (2), borderline patients did report overprotection as well as emotional neglect. The findings suggested that these experiences persist throughout childhood, and we did not attempt to determine whether they were in any way phase-specific.

We are, ourselves, practicing psychotherapists who have embarked on empirical studies in order to determine to what extent systematic inquiry can confirm clinical impressions. Progress in this field requires not more opinions but more research.

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JOEL PARIS, M.D.
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## Naltrexone Challenge for Hypercortisolemic Pseudodementia

SIR: Owen M. Wolkowitz, M.D., and associates (1) have shown in rigorous studies that corticosteroids produce a characteristic memory deficit. However, in speculating on the etiology of this effect, they overlooked one readily tested mechanism which is supported by a growing body of evidence, i.e., that corticosteroids induce memory impairment by activating the granular cells in the dentate layer of the hippocampus. Collier and Routtenberg (2) have already shown that when these cells are activated, they release granules of a memory-impairing endogenous opioid, and the memory impairment so produced can be blocked by opioid antagonists. Their further studies (3) confirmed that stimulation of the granular cell layer "activates the normal function of the granule cell system, resulting in erasure of information held in declarative memory." That the functioning of these cells varies with the serum cortisol level is suggested by studies like those of Sloviter et al. (4), who found that in adult mice hypocortisolemia causes dysfunction and degeneration of (only) these opioid-releasing granular cells. This hypothesis—that hypercortisolism produces its memory deficit by provoking the release of these stores of endogenous opioids—is uniquely attractive because it can be readily tested by the administration of opioid antagonists, which Collier and Routtenberg found prevented the memory impairment (2, 3).

A substantial body of work thus implicates degranulation of the hippocampal granular cells as responsible for cortisol-induced memory impairment, and this easily tested hypothesis should be investigated along with the other mechanisms proposed by Dr. Wolkowitz and his coauthors. If this hypothesis is confirmed, the reversal of memory impairment by challenge with an opioid antagonist like naltrexone would serve to detect those patients in whom this hippocampal system is intact, e.g., depressed patients whose memory impairment results from their hypercortisolemia. The reversal of memory impairment by naltrexone challenge could thus discriminate these "pseudodemented" patients from those whose dementia is accompanied by dysfunction or degeneration of the hippocampal granular cell system.

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## Dr. Wolkowitz and Dr. Reus Reply

SIR: We appreciate Dr. Lipschitz's thought-provoking letter in response to our recent article. Although caution must be exercised in extrapolating from animal studies to clinical situations, we agree that corticosteroid effects on the hippocampus may be important in determining their cognitive actions. In one of the studies cited by Dr. Lipschitz (his reference 4), adrenalectomy resulted in selective loss of hippocampal granular cells in rats; it remains uncertain, however, whether acute exogenous corticosteroid administration to intact subjects results in granular cell activation. Further, electrical stimulation of the granular cell layer in rats resulted in impairment of "declarative" memory (reference 2 in Dr. Lipschitz's letter); in the volunteer subjects in our study, exogenous corticosteroid administration led to a specific increase in commission errors without altering the rate of errors of omission in declarative memory tasks.

Nonetheless, Dr. Lipschitz's notion of opioid modulation of the cognitive effects of corticosteroids is quite interesting and worthy of further investigation. In an attempt to uncover such relationships, we recently found a series of correlations between corticosteroid-induced cognitive changes and changes in CSF and plasma biochemistry in the same subjects (1, and manuscript submitted for publication). We did not find any significant correlation between changes in cognitive performance and changes in CSF levels of β-endorphin or β-lipotropin. Rather, corticosteroid-induced cognitive changes were associated with changes in CSF or plasma levels of cortisol, ACTH, norepinephrine, 3-methoxy-4-hydroxyphenylglycol, and somatostatin-like immunoreactivity (manuscript submitted for publication).

The relation between changes in CSF levels of β-endorphin or β-lipotropin and focal changes in hippocampal granular cell opioid activity is unknown, and Dr. Lipschitz's suggestion of a pharmacologic blocking strategy (e.g., use of naltrexone) to test his hypothesis is intriguing and worth pursuing. We applaud attempts to discover the psychobiologic underpinnings of corticosteroid behavioral actions. In particular, Dr. Lipschitz's notion of attempting to differentiate pharmacologically between persons with transient corticosteroid-induced cognitive impairment and those with more permanent forms of dementia is commendable.

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OWEN M. WOLKOWITZ, M.D.
VICTOR I. REUS, M.D.
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## Administration of Anesthesia by Psychiatrists

SIR: I would like to expand on my position relating to psychiatrists giving anesthesia during ECT, as referenced by Theodore Pearlman, M.D., and his associates in the article "Should Psychiatrists Administer Anesthesia for ECT?" (1). I strongly agree with their position that psychiatrists are physicians who are, or should be, perfectly capable of handling simple medical procedures. The data on safety with ECT show that it is at least as free from danger as an intravenous pyelogram. No one, however, seems to feel that radiologists need medical assistance for this potentially lethal procedure. Apparently, they are better physicians than we psychiatrists.

I believe that much of this stems from "litigaphobia," an irrational fear of being sued (S.L. Brodsky, presentation at the annual meeting of the American Psychological Association, Washington, D.C., 1986). In 1987 I spent several weeks trying to clarify the exact extent of lawsuits relating to ECT. These data are virtually impossible to find; suits settled out of court are rarely reported, and unless appealed, most civil cases are unknown outside their own jurisdictions. I spoke to the vice-president of a professional liability corporation who agreed to discuss the matter with me off the record only. He was very honest about being unwilling to give me any hard data on what his company had paid for what claims, for fear that this would be used by attorneys to sharpen their aim in asking for settlements. For those who are willing to take my account on faith, what he said was that suits involving ECT are very rare, and when filed they almost always involve a major complication such as death. Psychiatrists were much more likely to be sued for medication errors or sexual misconduct. Most importantly, he was unaware of a single case in 20 years in which the specific issue was a psychiatrist's competence to administer anesthesia.

I was able to locate two significant suits. In one, a psychiatrist gave ECT to a patient who was known to have eaten and who aspirated food. No procedure is safe if improperly done. In the other case, the court ruled that ECT caused a patient's death, but an anesthesiologist had been in attendance and had left after the patient had "recovered." Where is the extra safety in this?

In my own experience, in a study of only 20 treatments, the actual time spent under anesthesia averaged less than 5 minutes when I was in charge of the anesthesia and more than 20 minutes when the same patient was assisted by an anesthesiologist (unpublished data). I also had a patient who chipped a tooth and demanded that she be repaid for the costs of repair. The anesthesiologist who was assisting me (because of a hospital ruling similar to that described by Dr. Pearlman and associates) flatly refused to pay this, stating that I was the physician in charge, even though I was not allowed to handle the airway.

If we are physicians, let us act like physicians and do what is clearly safe and vastly less expensive for our patients.

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JAMES F. HOOPER, M.D.
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SIR: As Bob Dylan said, "You better start swimmin' or you'll sink like a stone,/ For the times they are a changin'." Having cut my research teeth studying ECT anesthetic techniques (1–3), I feel moved to comment on the article by Dr. Pearlman and colleagues. I think we may need to make distinctions with respect to whether a physician *can, should,* or *must* perform a given procedure at a given time.

Being "qualified" to do something implies that a person *can* do it, within whatever parameters individual hospitals specify in their credentialing policies. Such parameters are not etched in stone. As Dr. Pearlman and associates pointed out, very few (if any) psychiatric residency programs currently provide enough anesthesia training to satisfy most hospital credentials committees. The argument that, for example, cardiologists or dentists are judged by a different standard, even from that for the psychiatrist who has been trained, may have some merit. I doubt we could easily win that debate given the relative infrequency with which ECT is used these days.

Does the fact that someone can do something necessarily mean that one *should* do it in a particular circumstance? The "should" also involves a medical-political question: Is the proper role of the specialist to adhere to specialist boundaries and collaborate with other specialists when boundaries overlap? Or is it to do as much as one feels capable of and only consult the other specialist when a problem is perceived? If I have the right (or obligation) to claim my professional territory, is not the same true for other specialties? ECT undoubtedly takes more time and lots more money when an anesthesiologist is present. But is that necessarily bad? What good is the time or money saved if a patient has a rare complication while under anesthesia administered by someone who is not prepared to manage it? What if someone who is prepared is down the hall or in the next room and that isn't close enough? I personally have found that collaborating with anesthesiologists for ECT has elevated my medical stature. It is another chance to show my colleagues that I can operate proficiently in an arena of medical specialization.

Finally, are there times when ECT anesthesia *must* be performed by the treating psychiatrist? For example, for patients in free-standing psychiatric hospitals that have no anesthesiologists on the staff and, perhaps, cannot get any? Is there evidence to support a position that ECT is sometimes (or ever) a life-saving emergency procedure that could not (or, in fact, should not) await the patient's transfer to a facility with anesthesiology services? I am not aware of such evidence. Whether or not such transfer capabilities are available may provide an exception. On the other hand, I personally know of a physician who died while receiving ECT under such a circumstance. He was an otherwise healthy, middle-aged man with a garden-variety depression. As far as I know, it was the only major ECT complication the psychiatrist had ever had. An anecdote rarely proves anything—unless you are the subject of it.

Where do I stand now? I certainly believe that any psychiatrist who administers ECT must be knowledgeable about the basic variables involved in the anesthesia. I believe that the psychiatrist should collaborate with the anesthesiologist in planning the optimum anesthesia regimen, and vice versa. A paper Dr. Smith and I wrote some years ago (4) was an attempt to promote such collaboration. I believe that the psychiatrist should not proceed with a treatment if there is any disagreement about the anesthesia regimen being used. I totally agree with Dr. Pearlman and his colleagues about the need to pay rigid attention to training, credentialing, and performance standards if psychiatrists are to be allowed to administer ECT anesthesia. I just think the time has passed when we *should* do it. And I cannot imagine a circumstance when I would think I *must* do it.

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CHARLES L. RICH, M.D.
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Sir: The article by Dr. Pearlman and associates captured my interest. I have practiced in the fields of psychiatry and anesthesiology for considerable periods of time and am Board certified in each.

First, it should be noted that the authors' figure of 8,161 cases is not impressive. These cases are short and relatively straightforward and should have minimal complications. If they have another 8,000 cases, it may be some cause for attention. It is an old saw, but anesthesia is only a means to an end.

If a psychiatrist wants to administer anesthesia, he or she should be willing to take the time to learn the techniques and principles to do it safely. After training many interns and residents, I would say that this would take 1–2 months on an active anesthesia service. The anesthetist should be able to do an endotracheal intubation on anyone and to manage any emergency that might arise.

After that, if the psychiatrist wants to assume the risks and insurance rates of an anesthesiologist, all I can say is, "Good luck."

PAUL S. JOHNSON, M.D.
*Fayetteville, N.C.*

Sir: In reference to Dr. Pearlman and associates' article, I should like to make a few comments.

First, I have been giving ECT since 1953 and therefore have over 35 years' experience, with approximately 100 treatments per year. During this time, working at a community hospital that is now a university medical center, I have been aware of only two serious complications, neither of which occurred with my series of patients. One was the death of a patient who was seriously disturbed and had just had an acute myocardial infarction; the second was a cardiac arrest for which the patient was successfully treated and recovered. Up until a few years ago, I administered anesthesia myself to low-risk patients.

In the state of New Jersey, the Department of Health has promulgated regulations for anesthesia that are quite rigid and restrictive. These regulations require that an anesthesiologist be available or on call to reach the hospital within 30 minutes under normal transportation conditions at all times. An anesthesiologist is defined as a Board-certified physician specialist. The regulations further state that during anesthesia, or even for patients receiving intravenous sedation while conscious, there must be monitoring of the blood pressure and pulse, respiration, ECG, and arterial blood oxygen saturation. They also require that the oxygen tension in the breathing circuit, the exhaled tidal volume, body temperature, and end-tidal carbon dioxide tension be monitored in patients receiving general anesthesia.

These regulations effectively limit the use of ECT to general hospitals. Even a local psychiatric hospital sends patients requiring ECT to a general hospital some 10 miles away. The state hospitals and most of the county hospitals do not use ECT and rarely send their patients to a general hospital to receive it. This prevents many of the patients who would most benefit from ECT from receiving it at all, since the physicians in the state hospitals generally do not have training or experience in the benefits of ECT; therefore, they are unlikely to recommend it.

I agree with Dr. Pearlman and associates that the restrictions on the use of anesthesia and ECT should be more flexible, for the benefit of the mentally ill.

GEORGE A. ROGERS, M.D.
*Camden, N.J.*

Sir: The article by Dr. Pearlman and associates underscored a dilemma that faced our facility for the past 2 years. Because we lost the services of an anesthesiologist for this interval, ECT was reserved for "exceptional" cases to be treated at a local community hospital. Given the population of over 2,000 inpatients, the lack of access to ECT was deemed to be of significant consequence. Luckily, after a protracted search we were able to recruit an anesthesiologist to join our staff. The restriction of our practice was largely dictated by the "community standard of care," which implied that anesthesia was to be administered by "qualified personnel," presumably anesthesiologists. In reality, numerous staff psychiatrists had previous training and experience in delivering anesthesia, and several had completed advanced cardiac life support certification.

It would be tremendously helpful for the APA Task Force on Electroconvulsive Therapy to address this controversy. Continued equivocation on this important issue raises the specter of increased liability, unnecessary restriction of psychiatric services, and unnecessary expense associated with this procedure. High-risk cases could be identified and triaged appropriately.

STEPHEN J. MASIAR, M.D.
*West Brentwood, N.Y.*

Sir: After reading the article by Dr. Pearlman and associates, I have misgivings about the authors' conclusion that psychiatrists should administer anesthesia for ECT. Although not Board certified, I did complete residency training in anesthesia and was in private practice for over a year before returning to finish a psychiatry residency. I am therefore in a much better position than most practicing psychiatrists to obtain anesthesia privileges for ECT. While I am sure that I could benefit financially from this situation, I would be loath to do so. Anesthesiologists and, under their supervision, nurse anesthetists are the experts in the administration of potentially lethal drugs such as succinylcholine and thiopental sodium. They are also superbly trained in management of the anesthetized airway and use these skills daily. Our patients deserve no less.

Several points made in the article disturbed me. Four endpoints were used in this retrospective study: fatalities, fractures, aspiration pneumonia, and post-ECT atelectasis. A recent study, which appears in Miller's *Anesthesia* (1), reported that mortality, while less than 1/10,000, is more than doubled in cases which are handled by surgeons and dentists as opposed to anesthesiologists or a combination of anesthetists and anesthesiologists. Further, although fatalities and fractures are clear endpoints, aspiration and atelectasis are not. How were these entities followed up, particularly in the 1,841 outpatients? What about other forms of morbidity, such as myalgias from succinylcholine or cardiac arrhythmias? Also, no mention was made of that rare but fatal anesthetic complication, malignant hyperthermia, and no mention was made of the monitoring used.

Another issue the authors discussed was anesthesia given by cardiologists, dentists, and gastroenterologists. My experience is that these specialists use intravenous sedation with benzodiazepines or narcotics. The patients' muscles of respiration are not paralyzed by succinylcholine, and they do not receive induction doses of thiopental sodium. This is qualitatively different from anesthesia for ECT. The comparison does not seem to hold up.

Competition between specialties was also reviewed by the authors. Their suggestion to give special anesthesia training to psychiatrists sounds suspiciously like the suggestion to give special pharmacology courses to psychologists so that they can prescribe psychoactive medications. Neither one is acceptable.

Finally, the negative image of psychiatry and ECT is repeatedly addressed. While this is indeed a problem, I question whether either psychiatry or ECT will be enhanced by psychiatrist-administered anesthesia, which is not the standard of care. Surely there are more effective ways of convincing our physician colleagues and the public at large of our value.

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CARLA RODGERS, M.D.
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Sɪʀ: Psychiatrists in the United States must squarely face the question of who should do ECT, and Dr. Pearlman and colleagues are to be commended for opening this debate. I agree with them that training is a critical issue. Patients are better served by physicians who are thoroughly trained in ECT, experienced in giving it, and interested in the process, regardless of their specialty. Indeed, Moscarillo (1) has proposed that cardiologists with specialty training should administer ECT anesthesia.

I disagree that the survival of psychiatry as a medical discipline has any relevance whatsoever to this debate. The guiding principle should be what is best for our patients. Given the profound physiological disturbances that occur during ECT (2) and the increasing technical complexity of the treatment (3), common sense would indicate that patients are better served by having available the expertise of both a psychiatrist and an anesthesiologist, provided both have had specialty training in ECT. We should aim for nothing less.

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## Dr. Pearlman Replies

Sɪʀ: I value the stimulating correspondence evoked by our article. Lively debate on the subject provides grist to the grindstone in the search for undistorted and effective standards of ECT anesthesia care.

Dr. Hooper's astute remark about litigation phobia, considering, as he points out, the paucity of ECT lawsuits, provides healthy objectivity to the discussion.

Dr. Rich, whose stated position is that our time for giving anesthesia for ECT has passed, has undoubtedly read Robert Browning's "The Pied Piper of Hamelin." For psychiatrists to swim en masse in a direction "piped" by those with motives other than quality ECT care is likely to bring psychiatry to "the river's brink, where it cannot come back to life I think."

I agree with Dr. Johnson, who is Board certified in psychiatry and anesthesiology, that psychiatrists doing ECT anesthesia should have training and experience in endotracheal intubation and emergency drug use. However, Dr. Johnson contradicts his message about the gravity of the risk that the psychiatrist assumes in administering anesthesia by his comment that our more than 8,000 cases in which patients were safely anesthetized are not impressive because "these cases are short and relatively straightforward and should have minimal complications."

Dr. Rogers and I agree that restrictions on the use of anesthesia and ECT operate to the detriment of many mentally ill patients. I agree with Dr. Masiar's suggestion that the APA Task Force on Electroconvulsive Therapy needs to avoid vacillating about who is qualified to administer anesthesia for ECT and to establish guidelines in support of psychiatrists' qualifications, based on rigorous training, for administration of ECT anesthesia.

Let me assure Dr. Rodgers that there is no financial benefit to psychiatrists administering anesthesia for ECT. Medicare, Medicaid, and private insurance reimburse psychiatrists for ECT under *CPT* code 1-90870 regardless of whether the anesthesia is given by a psychiatrist or an anesthesiologist. I take issue with Dr. Rodgers's argument that the superb training in airway management which anesthesiologists and nurse anesthetists receive is a reason why psychiatrists cannot do a similarly competent job. Dr. Rodgers might be loath to practice ECT anesthesia, and she has a professional right to avoid doing so. However, one unforeseeable day a patient—for example, one with alcohol dependency— may have an epileptic seizure in her office and require airway management which is similar to that for ECT. Lack of practice in airway management with ECT anesthesia might preclude sound airway management of the epileptic patient rendered unconscious by similar electrical activity in the CNS.

Dr. Rodgers correctly mentions malignant hyperthermia as a rare complication of succinylcholine administration. Such an unusual, life-threatening event will certainly require more than the presence of an anesthesiologist in addition to the availability of an anesthesia-administering psychiatrist to render emergency treatment. An entire intensive care unit treatment team will be necessary.

In rejecting the argument that it is unfair to restrict psychiatrists' anesthesia privileges but to allow cardiologists, gastroenterologists, and dentists to anesthetize or heavily sedate their patients, Dr. Rodgers loses sight of the fact that paralysis of respiratory muscles by succinylcholine is not the only manner by which respiration might be suppressed. Cardiologists, gastroenterologists, and dentists are fully aware of the CNS respiration-depressing effects of benzodiazepines and narcotics. Yet they competently, and without the same criticism from anesthesiologists, fulfill their anesthesia responsibilities.

Comparison by Dr. Rodgers of psychiatrists asking for ECT anesthesia privileges with psychologists clamoring for prescription privileges is hardly justified. Psychiatrists are trained in the basic sciences of medicine, including anatomy, physiology, and pathology of the brain, the heart, and the lungs, in addition to clinical monitoring of vital signs. Psychologists, who are experts in the evaluation and management of behavior, lack formal medical training.

Dr. Rodgers is wrong in implying that the standard of care is anesthesiologist-given anesthesia for ECT. The standard of the Joint Commission on Accreditation of Healthcare Organizations is that there should be uniformity in the quality of anesthesia care in the different departments of a hospital, including the departments of anesthesiology and psychiatry.

Finally, I disagree with Dr. Welch that the denial of ECT anesthesia privileges to psychiatrists has no relevance to psychiatry's future as a medical discipline. Once the technical competence of psychiatrists to do procedures relevant to their specialty is questioned, psychiatrists will be progressively denied the numerous incidental medical procedures (taking blood samples, suturing minor lacerations of elderly psychiatric patients who have fallen, doing spinal taps on psychotic patients with positive rapid plasma reagin test results) to the ultimate total demedicalization of the profession—other than prescribing psychotropic drugs and pressing ECT buttons!

THEODORE PEARLMAN, M.D.
*Houston, Tex.*

## Eating Disorders in Patients With Diabetes

Sir: We are grateful to Jean W. Helz, M.D., and Bryce Templeton, M.D. (1) for an interesting review of psychosocial factors in diabetes mellitus. However, we wish to draw their attention and that of *Journal* readers to one psychosocial problem associated with diabetes which was not mentioned. Specifically, we refer to the occurrence of eating disorders in young women with diabetes. Although epidemiological studies have not yet conclusively shown that diabetes is a risk factor for eating disorders, a recent review concluded that the greater part of the evidence points in this direction (2).

We found clinically significant eating disorders, based on *DSM-III* criteria, in almost 15% of a diabetes clinic population of female patients, ages 13–18 years, with insulin-dependent diabetes (3). In a subsequent study in the same clinic (4), we diagnosed bulimia nervosa, based on *DSM-III-R* criteria, in 5% of 103 female patients in the same age range. In the latter study, we also found that 12% of the total sample reported a history of intentional insulin undertreatment (i.e., complete omission or reduction of a scheduled dose) for the purpose of producing weight loss. In subjects with eating disorders, this method of weight loss was more commonly used than self-induced vomiting, extreme exercise, or laxative abuse.

In our experience, the presence of eating pathology in female patients with diabetes is often associated with significant problems with metabolic control. It also appears that in young women with diabetes, omission of insulin therapy to produce weight loss may be an important cause of impaired metabolic control. Indeed, we suggest that this possibility needs to be considered in all young women with poorly controlled diabetes.

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GARY RODIN, M.D.
DENIS DANEMAN, M.D.
*Toronto, Ont., Canada*

## Dr. Helz and Dr. Templeton Reply

Sir: We thank Dr. Rodin and Dr. Daneman for calling attention to this issue in diabetic patients. In our practices we have seen diabetic patients with important eating disorders; these disorders can easily represent an unrecognized complicating factor in the management of such patients.

It was not possible within the scope of our article to cover many important psychiatric issues in diabetes, but awareness of the possibility of eating disorders is clearly a special perspective the psychiatrist can bring to the treatment of the diabetic patient.

JEAN W. HELZ, M.D.
BRYCE TEMPLETON, M.D.
*Philadelphia, Pa.*

## Need for Polysomnographic Studies in Research on Disorders of Initiating and Maintaining Sleep

Sir: We congratulate Hugh Y. McClusky, M.A., and associates for their recent article entitled "Efficacy of Behavioral Versus Triazolam Treatment in Persistent Sleep-Onset Insomnia" (1). Studies of this nature have long been needed to clarify the roles of sedative-hypnotic therapy and behavioral techniques in the treatment of disorders of initiating and maintaining sleep. However, we do not believe that the findings in this study unequivocally support the authors' conclusion that "behavioral treatment is a viable alternative for persistent, psychophysiological, sleep-onset insomnia and may be preferable, considering its sustained effectiveness."

Given their method, it is not clear that Mr. McClusky and associates adequately defined a population of psychophysiologically insomniac patients by excluding other diagnoses. The authors claimed to have ruled out "nonpsychophysiological disorders of initiating and maintaining sleep such as restless leg syndrome, nocturnal myoclonus, and sleep apnea" without the use of polysomnography. They used a "Sleep Behavior Questionnaire [which] combined items in other questionnaires . . . that were found to correlate well with electrophysiological sleep measures." From a careful inspection of the authors' references, it appears that the Sleep Behavior Questionnaire was derived from two studies (2, 3) that did not use polysomnography and a third (4) that did not screen for myoclonus or sleep apnea. As a result, it is questionable whether Mr. McClusky and associates were successful in their attempts to screen out nonpsychophysiological disorders on the basis of their questionnaire data.

As we and others have shown, it is not possible to predict consistently the presence of such disorders as myoclonus or sleep apnea without using polysomnography (5, 6). While we encourage the initiative of Mr. McClusky and his colleagues, we cannot agree that their results are specific to psychophysiological insomnia, since their sample may have consisted of patients with a mixture of disorders of initiating and maintaining sleep. Unless studies of this type include polysomnographic screening, it will not be clear whether a particular treatment is effective for a specific subgroup of patients with disorders of initiating and maintaining sleep or for all such patients regardless of their diagnoses.

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W. VAUGHN MCCALL, M.D.
JACK D. EDINGER, PH.D.
*Durham, N.C.*

## Dr. Wooten Replies

SIR: There are several important factors to consider in response to the concerns raised by Dr. McCall and Dr. Edinger. All of the patients were screened for symptoms of any organic sleep disturbance by specific inquiry during the initial interview. An effort was also made to exclude patients who were more than 45 years of age because of the greater occurrence of sleep apnea and myoclonus in individuals older than 45 years. It might also be mentioned that a diagnosis of restless leg syndrome is arrived at by history, not by polysomnography.

Although it would have been ideal to use polysomnography in this study group to make absolutely sure of their diagnoses, the subjects were free of any symptoms of organic disorders, were not in an age group at significant risk for apnea or myoclonus, and did not have sleep maintenance insomnia that might suggest organic problems. It is also worthwhile to consider that most patients with chronic insomnia have developed secondary "conditioned" or "psychophysiological" features in addition to any underlying organic problems. Correcting underlying problems such as sleep apnea alone may not entirely relieve the complaint of insomnia, necessitating behavioral and/or pharmacological interventions (1). With regard to this final point, our subjects got better through the use of behavioral techniques; therefore, if any of them did happen to have organic problems, they still benefited from our interventions.

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VIRGIL WOOTEN, M.D.
*Little Rock, Ark.*

## Psychiatric Disorder and Bowel Disease

SIR: I read with great interest "Psychiatric Illness and Irritable Bowel Syndrome: A Comparison With Inflammatory Bowel Disease" by Edward A. Walker, M.D., and associates (1). The authors cogently discussed their finding of a high prevalence of psychiatric disorders in their group of patients with irritable bowel syndrome. They concluded that this group of patients might benefit from psychiatric evaluation and treatment.

The comparison group consisted of patients with inflammatory bowel disease. The authors found that the "lifetime prevalence of psychiatric disease in this group was low." At first glance the reader might conclude that emotional factors are not implicated in this disorder, since there is a low rate of psychiatric *disease.* I would like to address this issue as far as ulcerative colitis patients are concerned. Although findings are not conclusive, there have been articles in the literature which suggest that other *dimensions,* such as psychosocial aspects (2), alexithymia (3), and object relations (4), need to be explored.

Perhaps we need to look beyond the official psychiatric disorder—to understand the full human dimensions of stress, affect, and processes of internalization. If these factors can be seen as playing a role, perhaps therapeutic intervention may also be helpful with this patient population.

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ESTHER URDANG, A.C.S.W.
*Chestnut Hill, Mass.*

## Dr. Walker and Associates Reply

SIR: We appreciate the response of Ms. Urdang to our recent study. Although we would agree with her that many dimensions of psychosocial functioning in patients with irritable bowel syndrome need further study, we deliberately limited our investigation to the psychiatric aspects.

We would like to comment about one implication of Ms. Urdang's letter. We believe that the psychosocial aspects of many illnesses need to be further investigated. However, there appears to be a persistent belief that certain illnesses such as Crohn's disease and ulcerative colitis are unique in their association with a particular psychological state. Many of the psychosomatic hypotheses of clinicians such as Franz Alexander have not stood up to methodologically rigorous research. The low rate of psychiatric disease we found in the patients with Crohn's disease and ulcerative colitis does not indicate that they were not distressed. However, it may signal that these patients' level of distress did not reach the severity threshold which contributes to the expression of psychiatric disease. These data confirm earlier observations of Helzer et al. (1, 2) and suggest that patients with irritable bowel syndrome are in some way unique.

We appreciate Ms. Urdang's reminder of the impact of stress in the expression of physical disease and join with her in the expectation of further fruitful research in this area.

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EDWARD A. WALKER, M.D.
WAYNE J. KATON, M.D.
PETER P. ROY-BYRNE, M.D.
*Seattle, Wash.*

## Mechanism and Classification of Koro

SIR: In the article "Koro: Proposed Classification for *DSM-IV*" by Ruth L. Bernstein, M.D., and Albert C. Gaw, M.D. (1), the authors discussed the mechanism that I have proposed to explain the panic associated with koro. They erroneously mentioned my describing this series of events and experiences as "a self-incriminating causal loop." Perhaps this is a typographical error; I called it "a self-*incrementing* causal loop"(2):

> In societies in which the belief in *koro* is endemic, some men will be especially anxious about their penile states and hence will monitor them especially carefully. Many men from time to time experience the sensation of their penises shrinking as if retracting more than usual. (In the West, there are a number of jokes relating this experience to exposure to cold, usually cold water.) In cultural contexts which include a belief in *koro*, that experience will generate anxiety. Since the physiology associated with anxiety includes as one of its manifestations reduction of blood flow to the penis and consequent further penile retraction, perception of this retraction will further increase anxiety, frequency of monitoring, and frequency of receiving The Bad News. Frequently, receiving The Bad News will even further increase anxiety and its effects. This is an example of a self-incrementing causal loop.
>
> The specific meaning structure in which this loop is embedded will vary in differing cultural contexts. For this reason instances of the *Genital Retraction Taxon* will be most frequent in societies in which the endemic meaning structure most magnifies the anxiety. At times, for example when a rumor of a *koro* epidemic is circulating, this sequence of events will be experienced by enough men to generate a *koro* epidemic.
>
> However, since the originating experience is ubiquitous in all societies, similar instances will occur sporadically elsewhere, whenever the cognitive state of subjects for any reason generates anxiety sufficient to drive the loop.

I suspect such self-incrementing loops are common in a variety of contexts. For example, in discussing the ways in which self-consciousness affects social interaction, Erving Goffman (3) described just such a loop:

> To look self-conscious, then, is to break the cover of "looking like anyone else." But should the individual sense that his appearance is giving him away, he will feel that he has further cause to be fearful. Suppressing the urge to leave the field that this new fear creates will generate still further signs of unnaturalness which in turn will have their circular effect.

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RONALD C. SIMONS, M.D.
*East Lansing, Mich.*

SIR: In their review of koro, Dr. Bernstein and Dr. Gaw considered several possibilities for its classification in *DSM-IV* and proposed its inclusion in the novel category of "genital retraction disorder, culture-specific." Whatever the merits of placing koro in a unique diagnostic category, one clear hazard of this "splitting" is the concealment of the connections between koro and other diagnoses.

Others have proposed that disorders like koro should be lumped into the class of body dysmorphic disorders (1) or dysmorphophobia (2), diseases that appear to respond to serotonin reuptake blocking drugs (1) and to belong within the obsessive-compulsive disorder spectrum. Koro may well be a form of obsessive-compulsive disorder; segregating it into a unique class would obscure its unity with other somatoform disorders that also occur in sporadic, epidemic, and endemic fashion and would inhibit investigation of its response to the serotonergic drugs that are effective in treating other diseases of the obsessive-compulsive disorder spectrum.

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ALAN LIPSCHITZ, M.D.
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SIR: Dr. Bernstein and Dr. Gaw suggested adding the entity koro to *DSM-IV*. Hippocrates would presumably have called koro a cultural variant of hysteria, and among the pieces of dismembered hysteria now strewn in *DSM-III-R* and soon to fall into *DSM-IV*, there surely is at least one fragment that can accommodate koro nicely, obviate creating a redundant niche for it, and thereby serve the cause of nosologic parsimony.

WILLIAM F. SHEELEY, M.D.
*Phoenix, Ariz.*

## Dr. Bernstein and Dr. Gaw Reply

SIR: We appreciate Dr. Simons's pointing out our typographical error. We agree that the concept of a "self-incrementing causal loop" is relevant not only in koro but in many other disorders marked by a panic component.

We strongly considered body dysmorphic disorder but dismissed it for the following reason. Body dysmorphic disorder is defined as a "preoccupation with some imagined defect in appearance in a normal-appearing person" (*DSM-III-R*). Typical is a person preoccupied with the size of his nose who has a history of repeated visits to plastic surgeons in an effort to correct the imagined defect. Marked disruption of function is uncommon. In fact, the central concern in koro, the fear of genital retraction and impending death, is not with the appearance of the genitals but, rather, with their dissolution. Panic or anxiety invariably accompanies the fear of genital retraction and resultant death. Marked disruption of function is common, and the presentation of koro symptoms is acute, dramatic, and clearly linked to cultural beliefs.

Although koro has certain hysterical features, we did not consider the term "hysteria" because it has been omitted from the current system of classification.

RUTH L. BERNSTEIN, M.D.
ALBERT C. GAW, M.D.
*Bedford, Mass.*

*Reprints of letters to the Editor are not available.*

## Correction

In the article "Suicide, Stressors, and the Life Cycle" by Charles L. Rich, M.D., et al. (April 1991 issue, p. 524), the second author's name is misspelled. Gary M. Warstadt, M.D., is the second author of this paper.

# *APA Official Actions*

# Quantitative Electroencephalography: A Report on the Present State of Computerized EEG Techniques

American Psychiatric Association Task Force on Quantitative Electrophysiological Assessment

*The American Psychiatric Association established the Task Force on Quantitative Electrophysiological Assessment*[1] *in May 1989 to consider several questions of interest to psychiatrists. From the inception of techniques for quantitative electroencephalography (qEEG), the possibility was raised that it would substantially assist in the diagnosis of brain disorders. However, controversy exists over the scientific basis for such approaches and the training necessary for interpretation of computerized records. The task force's charge was to report 1) the present state of scientific knowledge about qEEG, 2) the role for qEEG in clinical psychiatric practice at the present time, 3) the training necessary for the use of qEEG techniques, and 4) the possible future of the technique in the study of mental disorders. The task force concluded that qEEG is particularly useful for the detection of abnormalities in slow waves, which are a feature of delirium, dementia, intoxication, and other syndromes involving gross CNS dysfunction. The ability of qEEG to help in the diagnosis of other disorders, such as schizophrenia or depression, is not yet established. Clinical replications and sharing of normative and patient data bases are necessary for the advancement of this field. Proper use of this technique requires extensive training in a center experienced in its use. Standards for training and for using the technology in psychiatry are urgently needed.*

*This report was approved by the Board of Trustees in December 1990.*

The American Psychiatric Association (APA) established the Task Force on Quantitative Electrophysiological Assessment in May 1989 to consider several questions of interest to psychiatrists. From the inception of techniques for quantitative electroencephalography (qEEG), the possibility was raised that it would substantially assist in the diagnosis of brain disorders (1, 2). However, controversy exists over the scientific basis for such claims, the value of computerized measurements versus traditional EEG approaches, and the training necessary for interpretation of computerized records (3, 4). Unfortunately, advertisements and promotional material from some manufacturers of qEEG instruments have gone beyond the existing scientific evidence to make claims of diagnostic utility. The task force's charge was to report 1) the present state of scientific knowledge about qEEG, 2) the role for qEEG in clinical psychiatric practice, 3) the training necessary for the use of qEEG techniques, and 4) the possible future of the technique in the study of mental disorders. This report will review the technique itself and then discuss the points addressed by the task force.

## QUANTITATIVE EEG TECHNIQUE

Electrical activity originating in the brain can be recorded from the surface of the scalp by using conventional EEG techniques to provide 1) analysis of the spontaneous EEG and 2) analysis of the brain activity evoked by a stimulus. Recordings of at least three kinds of brain electrical activity have clear clinical utility. The sudden activation of large groups of neurons, as occurs during epilepsy, is reflected in abnormal spike activity. Disturbances in the normal cerebral cortical rhythms, as occurs in patients with dementia and other organic brain syndromes, are reflected in decreased frequency and increased prominence of slow waves in the EEG. Disturbances in specific brain pathways, such as the optic neuritis of multiple sclerosis, are reflected in changes in sensory evoked potentials. Electrical activity is generally recorded from many sites over the scalp to assist in localizing changes in underlying brain areas. The activity from each electrode is plotted on a chart record, which can be voluminous because of the multiple recording sites and the many minutes of recording time. Analysis by an electroencephalographer requires knowledge of the normal patterns of activity of the brain in various behavioral conditions, such as waking and sleep, as well as recognition of artifacts caused by factors such as body movement and electrical interference.

Quantitative EEG involves the use of digital computer technology to improve the analysis of the EEG in three ways. First, a power spectrum is calculated for each recording site. This approach, a variant of Fourier analysis, treats the EEG as the sum of waves of various frequencies, i.e., slower waves and faster waves summed together. The power spectrum quantitates the amount of activity at each frequency. From such a spectrum, one can determine if a particular type of wave, such as alpha, is present to a normal degree. This method is a potential improvement over looking at the EEG waves on paper records; in that case, various waves are mixed together, so no quantitative assessment can be made. For example, small amounts of EEG slowing are often difficult to detect in manual analysis. On the other hand, the computer method has the potential drawback that only a brief segment is shown, whereas conventional EEG records display many minutes of activity, which provide an opportunity to detect rare abnormal events.

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[1] The members of the task force are Robert Freedman, M.D. (chairperson), Daniel J. Luchins, M.D., Robert W. McCarley, M.D., and John M. Morihisa, M.D. The task force appreciates the input provided by Robert Cancro, M.D. The task force was staffed by Harold Alan Pincus, M.D., and Wendy Davis, M.Ed.

The second technique provides a visual image in the form of a map over the surface of the head. These colorful maps attract attention in research papers, clinical reports, and advertisements. The computer constructs these maps by selecting a particular frequency and color coding the amplitude in the power spectrum for each EEG lead. Hot colors, such as red, represent high amplitude, and cool colors, such as blue, represent low amplitude. Between the recording sites, the computer interpolates values to provide a continuous map over the entire head. Thus, if the alpha activity of a normal subject is plotted, one might see a red (hot) area over the posterior head near the occipital lobes. In the initial reports of this technique it was called "brain electrical activity mapping" (BEAM) (1). The potential advantage of this approach is that patterns such as hemispheric asymmetry can be more easily spotted because one sees the data displayed over the surface of the head in color. An abnormally high frequency of slow waves over the frontal lobes, found in some dementias, might be difficult to see in paper records but would be obvious on a color-coded map.

The third strategy is to compare the maps, or the electrical activity on which they are based, by various statistical techniques. An individual patient's values at each point on the scalp are compared with those of a known group, either normal subjects or subjects with a specific illness, such as schizophrenia. The values are often analyzed statistically by calculating the z score, the difference between the patient and the comparison group, divided by the group's standard deviation. These z scores are then color coded to form a new map, which emphasizes areas in which the patient differs from the comparison group. These "significance probability maps" are also frequently displayed in advertisements. A problem is that these z statistic maps involve multiple comparisons and thus can suggest statistical significance when it is not present.

A more sophisticated approach is the use of multiple discriminant analyses. Quantitative EEG data for groups of normal and mentally disordered subjects are recorded to form qEEG data bases, in which each subject is represented by many recording sites and each site has different amplitude values for many frequencies. Given the complexities of brain function, the disturbances that are the pathophysiological bases of mental disorders may not be apparent in a single power spectrum or even in maps of particular frequencies. The discriminant analysis approach allows the construction of complex functions that would discriminate between groups, by summing very small distinctions into larger, more statistically significant differences. An analogy could be drawn to psychiatric diagnosis itself, in which single symptoms themselves carry little weight but a combination - e.g., depressed mood, weight loss, sleep disturbance, decreased energy, and ideas of worthlessness - form a complex with much higher predictive value. The potential advantage of this approach is that, given an adequate data base, the computer might be able to determine if an individual had a qEEG that was typical of a particular clinically defined disorder, if it were assumed that each illness has a unique pattern of brain activity as determined by scalp recording.

One potential disadvantage is that multiple discriminant analysis cannot determine if the features it extracts are of fundamental biological or psychological importance. This limitation is particularly troublesome because EEG measures themselves are only indirect measures of neuronal activity and 1) are subject to subtle artifacts from nonneuronal sources and 2) may represent trivial correlates of the disorder in the population being examined. An example of a trivial correlation would be a high prevalence of higher EEG frequencies in a group of acutely psychotic schizophrenic patients, which might simply be due to their high level of stress. From the data on these patients, the computer might categorize all patients with high-frequency activity as schizophrenic. However, this feature is not typical of schizophrenic patients in remission and can be found in anxious nonschizophrenic patients as well. Only a very large body of data, carefully collected from many centers and analyzed with rigorous clinical and statistical methods and proper control for artifacts, can prevent such adventitious, but ultimately spurious findings.

Critical features of all statistical comparisons are the quality of the recordings and the actual normality of the normal comparison group. Many instrument manufacturers offer a normative data base for comparisons with the patient data. However, these data bases are of variable quality and, because of their proprietary origin, have generally not been subjected to the usual scientific scrutiny. Details about diagnostic procedure, recording technique and artifact control, and the distribution of individual scores are inadequate. Many of these deficiencies could be lessened if the missing information and the raw data from the individuals constituting the data base were provided. If these features were available and if the data bases were in the public domain, normal peer review would highlight any biases and deficiencies in the data base. The task force is currently unable to endorse any available data base because this information is lacking.

## SCIENTIFIC FINDINGS

The qEEG technique has been extensively used to study physiological changes in the brains of patients with neurological and mental illnesses. Examples of the more than 100 studies that have used these techniques are comparisons of patients with normal subjects that indicated more delta waves in schizophrenic patients (5), differences in beta activity in alcoholics (6), and more delta and theta waves in patients with Alzheimer's dementia (7). Research with the mapping technique for evoked potentials has also yielded useful findings. For example, the maps and multivariate feature characterization demonstrate focal abnormalities in left temporal scalp regional activity in schizophrenia that are associated with temporal lobe structural abnormalities (8). Frontal scalp regional abnormalities are present in obsessive-compulsive disorder (9). The mapping technique has also been used to demonstrate actions of psychotropic drugs by measuring their effect on brain activity (10).

Most of these studies have used qEEG to help define and localize a particular abnormality in brain activity as part of the study of the pathophysiology of a specific illness. However, only a few studies have suggested that qEEG findings correlate with clinical diagnoses. Such studies have not concentrated on particular pathophysiological features but, rather, have used discriminant analysis. Shagass et al. (11) found that the variables derived from EEG recordings could discriminate between some illnesses, diagnosed initially with *DSM-II* criteria. For example, latent schizophrenia, which they equated with *DSM-III* borderline and schizotypal personality disorders, was distinguished from neuroses with a sensitivity of 60% and a specificity of 92%. If the two disorders were equally frequent, the computer could match the clinical diagnosis in 88% of the cases. Shagass et al. suggested that this technique might have particular value for distinctions between pairs of conditions that are difficult to resolve clinically. John et al. (2, 12) described a similar strategy for discriminant analysis with the qEEG technique, which they termed "neurometrics." Using discriminant analysis, they were able to construct a formula that classified 212 subjects as normal or as having primary depression, alcoholism, or dementia with concordances to clinical diagnosis ranging from 72% to 80%. A replication with 166 subjects achieved similar results with the same formula. The technique was also used to separate unipolar and bipolar depressed subjects; 85% of each group were assigned to the appropriate clinical categories. Whether or not these distinctions can be generalized to nonresearch conditions has not been established.

## CLINICAL USE

Various instruments are now commercially available for qEEG determinations. These instruments, with appropriately trained operators, are capable of producing high-quality EEG records, accurate power spectra, and color-coded maps. These maps are useful for determination of abnormal slow wave activity. They are less useful for detection of seizure activity. The instruments used for different functions have similar hardware but different software. Also, the manufacturers differ in their advertised claims of clinical utility. At this time, the ability of any qEEG procedure to make psychiatric diagnoses or to discriminate between various groups of psychiatric patients and normal subjects is not well established.

The most valuable clinical role seems to be the evaluation of conditions likely to involve slow wave abnormalities, i.e., stroke, dementia, delirium, and intoxication. EEG recordings have traditionally been part of the evaluation of these conditions, although one survey of psychiatric practice suggests that the results are rarely relied on for differential diagnosis (13). In only one study were readings of paper EEG records by a clinical electroencephalographer compared with interpretation of a qEEG map (14). In that study the qEEG was slightly more sensitive than routine EEG for detection of abnormalities in 100 consecutive patients referred for recording.

## TRAINING FOR USE AND INTERPRETATION

There are no generally agreed on standards for the training of psychiatrists who perform qEEG or interpret qEEG records. Artifact-free recording requires experience in electrode application and elimination of common artifacts, such as artifact from ECG, muscle tension, or eye movements. This technical ability is likely to require performance of 50 or more recordings under the supervision of experienced personnel. Interpretation of the qEEG record requires substantial clinical experience. Extensive experience in a center devoted to such recordings and clinical interpretation of qEEG records is necessary. The user of these data must understand that the increased power of these techniques also increases their potential for misinterpretation (4, 15, 16). Training should include comparison of qEEG records with other data and with clinical outcome. Because qEEG itself contributes only limited information of direct clinical significance, persons otherwise not qualified to perform differential diagnoses of mental disorders are not qualified to make diagnoses with qEEG. Because the current uses of qEEG and the current uses of conventional EEG have somewhat different purposes and advantages, it is not clear that all users of qEEG need to be certified electroencephalographers (17), although some electroencephalographers have suggested such a requirement (18). However, the qEEG user must know the strengths and limitations of qEEG compared to conventional EEG. Although weekend training courses are offered by several of the instrument manufacturers, these brief sessions are not sufficient for learning how to perform qEEG and interpret qEEG records. Instead, appropriate training programs and certification criteria for qEEG are needed for psychiatrists who wish to use the technique. Additional efforts should be made to provide general education about the technique in residency training and in postgraduate courses.

There is also no certification by the U.S. Food and Drug Administration or other governmental agency of the instruments themselves or of the indications for their use in clinical practice. Their proper use in an individual clinical practice is therefore the ethical responsibility of the physician. In addition to this report, there are similar reports from other professional societies concerned with the use of qEEG (19, 20). Although they differ in specific recommendations, these reports express similar concerns about establishment of scientific and clinical bases for the use of qEEG and about proper standards for the training of those who use the techniques.

## FUTURE SCIENTIFIC DIRECTION

Quantitative EEG is a technique of great promise that should have a place along with other brain imaging techniques in research on brain illnesses. In conjunction with magnetoencephalographic recording (MEG), it has potential usefulness in the localization of the sources of abnormalities in brain electrical activity, which are part of the pathophysiology of many brain disorders. Findings obtained with qEEG have greater power when they are correlated with other biological features, such as underlying structural changes revealed by other techniques, such as computed tomography (21) and magnetic resonance imaging. Such investigations will probably increase our understanding of the pathogenesis of mental disorders and thereby perhaps lead to better diagnoses. The technique may also have utility in the monitoring of response to psychotropic agents and other treatments. Psychiatrists hope that the successful use of qEEG for detection of slow wave abnormalities in organic brain disorders may be extended some day to the detection of abnormal features in such illnesses as schizophrenia and affective disorder. Such investigations may lead to better diagnostic systems and more objective criteria for classification. These investigations are already being conducted in several research centers with support from the National Institute of Mental Health, the Medical Research Service of the U.S. Department of Veterans Affairs, and other sources. As with most other research efforts, their quality is monitored by scientific peer review, both at the time of funding and at the time of publication of the results in scientific journals.

## SUMMARY

Quantitative EEG has been proposed as a diagnostic aid for psychiatric practice. It has particular utility for the detection of abnormalities in slow waves, which are a feature of many organic brain syndromes.

The ability of qEEG to assist in the diagnosis of other disorders, such as schizophrenia or depression, is not yet established. Clinical replications and sharing of normative and patient data bases are necessary for the advancement of this field. Proper use of this technique requires extensive training in a center experienced with its use. Establishment of standards for training and for the use of the technique in psychiatry are urgently needed.

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# Guidelines for Psychiatric Practice in Community Mental Health Centers

*This is a task force report issued jointly by the APA Task Force on Professional Practice Issues in Organized/Managed Care Settings*[1] *and Assembly Task Force on Community Mental Health Centers.*[2] *It was approved by the Assembly of District Branches in May 1988 and by the Board of Trustees in December 1988.*

This report deals with an important subject that directly affects the mental health care delivery system and its impact on the many Americans who receive such care at community mental health centers (CMHCs) throughout the country. The American Psychiatric Association (APA) is committed to the principle that the provision of quality services should be the overriding goal in the delivery of care and treatment to all patients suffering from mental illness. While APA believes that the training and experience of any health care provider obviously have an important relationship to this goal, it nevertheless recognizes that the decision as to how best to provide quality care in a particular CMHC must ultimately be made by that center's governing board, subject to any limitations imposed by state or federal law. In particular, this report focuses on the appropriate provision of psychiatric services in such settings and is not intended to define or describe the role of nonpsychiatrists. Any center which relies on this report should assure that it has made an independent decision to do so on the basis of its own needs and policies, ultimately ascertained and developed by its governing board.

## GUIDELINES FOR PSYCHIATRIC PRACTICE

Psychiatric care in CMHCs[3] is delivered through the combined expertise of multidisciplinary teams that include, among others, nurses, psychiatrists, psychologists, and social workers. The multidisciplinary approach is vital to the provision of comprehensive care within these settings. The effective delivery of this care requires both mutual appreciation of each discipline's special expertise and full interdisciplinary cooperation.

Several factors, outlined later in this statement, affect the role of psychiatrists working in CMHCs, and these guidelines set forth APA's view as to the appropriate role of psychiatrists in CMHCs.

1. The care of seriously and persistently mentally ill patients[4] is increasingly the responsibility of CMHCs, thus requiring CMHCs be true medical care facilities.
2. Mentally ill patients require comprehensive differential diagnostic evaluation, comprehensive and integrated treatment planning, and medical management in all three of the biological, psychological, and social spheres.
3. Medical problems that are potentially life threatening can manifest themselves as psychiatric problems requiring prompt diagnosis, treatment, and management.
4. The treatment of mentally ill patients frequently requires medical management that includes the prescription of medication or other somatic therapies, which often require physical and physiological preparatory workups and continued monitoring for side effects and toxicity.
5. Physicians in the medical specialty of psychiatry have the medical training and skills needed to evaluate physical problems and the relationship of physical problems to psychological and social phenomena.
6. The physician is usually held legally responsible for the medical/psychiatric care provided in his or her service delivery system and should have authority appropriate to that responsibility.

It is clear, therefore, that to ensure quality care for patients with severe mental illness, a CMHC must provide appropriate medical/psychiatric services[5] for patients. To further this goal, APA recommends that ultimate responsibility for the clinical care of patients in such facilities be placed in a medical director who is fully trained and qualified to provide appropriate supervisory oversight with respect to diagnosis, treatment planning, and clinical services for all patients.

## MODEL JOB DESCRIPTIONS

### *Medical Director*

Unless the chief executive officer (CEO) is properly trained and qualified to serve this purpose, the medical director has the ultimate authority and responsibility for the medical/psychiatric services of the center. Specifically, this includes responsibility for the following.

1. Assuring that all center patients receive appropriate evaluation, diagnosis, treatment, medical screening,[6] and medical/psychiatric evaluation whenever indicated.
2. Assuring that clinical staff receive appropriate clinical supervision.
3. Overseeing the work of all physicians, including residents assigned for training.
4. Assuring appropriate implementation of clinical staff development and staff training activities.
5. Assuring, through a multidisciplinary process, the appropriate privileging and regular performance review of all clinical staff.
6. Providing direct psychiatric services.

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[1] The members of the Task Force on Professional Practice Issues in Organized/Managed Care Settings were Haroutun Babigian, M.D. (chairperson), Kenneth D. Gaver, M.D., Jonathan F. Borus, M.D., Judith L. Feldman, M.D., Gordon H. Clark, Jr., M.D., Don E. Flinn, M.D. (consultant), Alan I. Levenson, M.D. (consultant), Captane P. Thomson, M.D. (corresponding member), Daniel Y. Patterson, M.D. (corresponding member), Richard T. Rada, M.D. (corresponding member), Benjamin M. Ianzito, M.D. (corresponding member), Rena M. Nora, M.D. (corresponding member), Alexander R.H. Rodriguez, M.D. (corresponding member), and Irvin D. Milowe, M.D. (Assembly liaison).

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[3] A CMHC is a community agency that renders active treatment and psychosocial rehabilitation to patients in the community without regard for their ability to pay.

[4] A mentally ill patient is an individual who has one or more of the mental disorders described in APA's *Diagnostic and Statistical Manual of Mental Disorders (Third Edition - Revised) (DSM-III-R)* and who is in active treatment.

[5] "Medical/psychiatric services" is used broadly to indicate the clinical care provided to persons with mental disorders either by psychiatrists or under their direct supervision.

[6] Medical screening is the determination upon intake of the need for physical examination and/or laboratory studies. The development of the center's medical screening process is the responsibility of the medical director. The medical screening may well indicate the need for further diagnostic studies and/or specialty consultation.

7. Advising the CEO regarding the development and review of the center's programs, positions, and budgets that affect clinical services.

8. Assisting the CEO by participating in a clearly defined and regular relationship with the board of directors.[7]

9. In cooperation with the CEO, participating in regular and direct communications with the office of the state mental health program director, when appropriate, regarding psychiatric issues.

10. Providing liaison for the CMHC with community physicians, hospital staff, and other professionals and agencies with regard to psychiatric services.

11. Developing and maintaining, whenever possible, all educational programs in concert with various medical schools and educational programs.

12. Assuring the quality of treatment and related services provided by the center's professional staff, through participation (directly or by designee) in the center's ongoing quality assurance and audit processes.

The medical director, by licensure, training, and prior clinical/administrative experience, should be qualified to carry out these functions. The medical director should be employed full time, and at least half of his or her time should be allocated to direct clinical care and clinical oversight.

### *Staff Psychiatrist (Full- or Part-Time)*

The staff psychiatrist has authority and responsibility for psychiatric services of the center assigned to him or her by the medical director or, when appropriate, by the CEO. Specifically, this includes responsibility for the following.

1. Providing direct psychiatric services through comprehensive evaluation, diagnosis, treatment planning, and treatment for patients assigned to him or her.

2. Assuring that clinicians in services assigned to him or her receive appropriate clinical supervision.

3. Participating in administrative duties as assigned, which could include, for example, being a member of or chairing the quality assurance and/or utilization review committees.

## GUIDELINES FOR EVALUATION AND TREATMENT OF PATIENTS

1. Each newly evaluated patient should be medically screened, and the patient's history should be reviewed to assure that the full range of medical considerations is taken into account in determining the diagnosis and appropriate treatment.

2. A psychiatrist may prescribe or adjust psychotropic medication only after his or her direct evaluation of the patient (except when the psychiatrist is covering for an absent colleague whose patient requires a minimal refill on an existing prescription).

3. Each patient with a stable medication regimen should be evaluated directly by a psychiatrist at least every 3 months.

4. The frequency, process, content, and duration of any psychiatric evaluation/intervention should be based on patient need and not on administrative or fiscal considerations.

5. Utilization review of all patients in continuing care should include appropriate medical/psychiatric participation.

## GUIDELINES FOR PRACTICE IN EMERGENCY SERVICES

1. Clinical responsibility and authority for the emergency service should ultimately rest with the medical director, who should assure that these services are provided by fully trained and qualified personnel.

2. A psychiatrist should always be available by telephone and, as appropriate, for face-to-face evaluation of patients in the emergency service.

3. The cases of all patients who come to the CMHC emergency service should be reviewed by a psychiatrist (through oral report or written record) by the next working day to assure that all patients receive appropriate medical screening.

4. If a patient seen in the emergency service is hospitalized, the center's emergency service should provide appropriate clinical information to the staff of the admitting hospital.

## THE PSYCHIATRIST'S RESPONSIBILITIES IN A MULTIDISCIPLINARY TEAM

In fulfilling the medical responsibilities in a mental health center, a psychiatrist's work with other clinicians serves the following important functions.

1. To assure that the medical/psychiatric services provided meet the prevailing professional standards.

2. To help develop and review clinical treatment plans.

3. To provide regular opportunities for collaboration by psychiatrists and other professional staff concerning patients they are treating in common.

4. To inform and educate other clinical staff in salient aspects of patient health, the relationship of psychosocial and physiological problems, and the appropriate use of psychotropic medications, their side effects, toxicity, etc.

5. To provide support for clinical staff by sharing responsibilities, experiences, and skills in dealing with severely disturbed patients.

All clinical staff should, therefore, have regularly scheduled time to discuss issues related to appropriate patient care.

## GUIDELINES REGARDING PSYCHIATRISTS' SIGNATURES

1. A psychiatrist's signature on any report or reimbursement form indicates that he or she has accepted medical responsibility for the patient. Such reports or forms should clarify whether the psychiatrist served as the direct provider, supervisor, consultant, or reviewer with respect to the care and treatment in question.[8]

2. A psychiatrist should sign insurance or other reimbursement forms, in compliance with general requirements, only for patients whom he or she has directly evaluated or fully reviewed with the treating clinician.

## GUIDELINES FOR PSYCHIATRIC STAFFING

1. Psychiatric staffing should be adequate to carry out the psychiatric functions defined in this document.

2. The guidelines for CMHC psychiatric staffing should meet the prevailing medical standards and any state standards for each of the different treatment settings in the CMHC network (e.g., inpatient, outpatient, emergency/crisis, partial hospitalization, residential services).

## REFERENCE

1. Guidelines for psychiatrists in consultative, supervisory, or collaborative relationships with nonmedical therapists (official actions). Am J Psychiatry 1980; 137:1489–1491

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[7] Center CEOs are encouraged to have their medical directors regularly attend board of directors meetings. Hospitals do so with their presidents and medical chiefs of staff. CEOs thus assure that their boards are afforded clinical/medical input, thus maximizing program quality and minimizing liability risk.

[8] As stated in APA's "Guidelines for Psychiatrists in Consultative, Supervisory, or Collaborative Relationships With Nonmedical Therapists" (1), "In a supervisory relationship [with a nonmedical therapist who provides services to the patient] the psychiatrist retains direct responsibility for patient care and gives professional direction and active guidance to the therapist. In this relationship the nonmedical therapist may be an employee of an organized health-care setting or of the psychiatrist. The psychiatrist is clinically responsible for the initial workup, diagnosis, and prescription of a treatment plan, as well as for assuring that adequate and timely attention is paid to the patient's physical status and that such information is integrated into the overall evaluation, diagnosis, and planning. The psychiatrist remains ethically and medically responsible for the patient's care as long as the treatment continues under his or her supervision."

THE AMERICAN JOURNAL OF PSYCHIATRY

*Special Articles*

# A Current View of the Interface Between Borderline Personality Disorder and Depression

**John G. Gunderson, M.D., and Katharine A. Phillips, M.D.**

*The recent and dramatic expansion in studies about borderline and depressive disorders is reviewed with respect to the implications about their interface. Revisiting this subject 6 years after an earlier review reveals that intervening research has altered the conclusions that should be drawn. Growing evidence from family history, comorbidity, phenomenology, psychopharmacology, biological markers, and a new domain, pathogenesis, indicates that a surprisingly weak and nonspecific relationship exists between these disorders. Implications are drawn with respect to classification, therapeutics, and defining the borderline construct.*

(Am J Psychiatry 1991; 148:967–975)

Although empirical evidence has helped to clarify the relationship between borderline personality disorder and depression (1), the interface between these disorders remains incompletely defined. The interface retains its interest for clinicians because patient treatment is often influenced by how this boundary is viewed.

This paper begins where a 1985 review on the interface between borderline personality disorder and affective disorder left off (1). At that time, four explanatory hypotheses on the relationship between these two disorders were identified (table 1): I: depression is primary and can produce signs and symptoms of borderline personality disorder, II: borderline personality disorder is primary and can produce signs and symptoms of affective disorder, III: they are unrelated, and IV: they are related but in a nonspecific fashion. The evidence available at that time generally favored hypothesis IV, i.e., that both disorders share mixed nonspecific etiologies. Since then, neither the relatively modest additions to the psychodynamic literature nor the significant new studies on course of illness (2, 3) have altered that review's conclusion. In contrast, as shown in table 2, more recent evidence on comorbidity, phenomenology, family history, pharmacotherapy, biological factors, and a new domain, pathogenesis, leads to new conclusions about this interface. That is the subject of this review.

## COMORBIDITY ISSUES

In 1985, the recurrent finding that patients with borderline personality disorder have a high prevalence of depression was seen as evidence that these two disorders are closely linked (table 1). Yet such comorbidity studies are hard to evaluate because four of the criteria by which borderline personality is diagnosed in *DSM-III* and *DSM-III-R* are related to the affective domain, i.e., affective instability, chronic emptiness and boredom, intense anger, and recurrent suicide overtures. Hence, the finding of comorbidity may be circular, reflecting definitional artifact based on these shared criteria.

The subsequent finding that other axis II disorders (whose definitions include less depressive symptoms) have equal or higher frequencies of concurrent or life-

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**TABLE 1. Evaluation of Four Hypotheses About the Interface Between Borderline Personality Disorder and Depression in 1985**

| Hypothesis | Comorbidity | Phenomenology | Family Prevalence | Drug Response | Biological Factors | Course | Psychodynamic Factors |
|---|---|---|---|---|---|---|---|
| Depression is primary (it can produce signs and symptoms of borderline personality disorder) | Supports | Refutes | Refutes | Strongly refutes | Supports | Strongly refutes | Mixed |
| Borderline personality disorder is primary (it can produce signs and symptoms of depression) | Supports | Supports | Refutes | Supports | Mixed | Refutes | Supports |
| Depression and borderline personality disorder are unrelated | Strongly refutes | Refutes | Strongly supports | Refutes | Supports | Supports | Refutes |
| Both disorders have overlapping, nonspecific sources | Supports | Strongly supports | Strongly supports | Strongly supports | Supports | Supports | Mixed |

**TABLE 2. Evaluation of Four Hypotheses About the Interface Between Borderline Personality Disorder and Depression in 1990**

| Hypothesis | Comorbidity | Phenomenology | Family Prevalence | Drug Response | Biological Factors | Pathogenesis |
|---|---|---|---|---|---|---|
| Depression is primary (it can produce signs and symptoms of borderline personality disorder) | Refutes[a] | Refutes | Strongly refutes[a] | Strongly refutes | Strongly refutes[a] | Mixed[a] |
| Borderline personality disorder is primary (it can produce signs and symptoms of depression) | Refutes[a] | Supports | Strongly refutes[a] | Strongly supports[a] | Refutes[a] | Mixed[a] |
| Depression and borderline personality disorder are unrelated | Supports[a] | Supports[a] | Strongly supports | Supports[a] | Strongly supports[a] | Supports[a] |
| Both disorders have overlapping, nonspecific sources | Supports | Strongly supports | Supports[a] | Supports[a] | Mixed[a] | Mixed[a] |

[a] These evaluations changed from 1985 to 1990.

time depression (4–7) supports the conclusion that the comorbidity between these two disorders is nonspecific—or, at most, incidental to the overlap of the definitions of borderline personality disorder and affective disorder. Zanarini et al. (6) found a high frequency (80% lifetime history) of major depression in their patients with both dysthymia and borderline personality disorder but then showed that this association may be nonspecific, since the lifetime rate of major depression in patients with other types of personality disorder was equally associated with the presence of dysthymia.

Research using depressed samples as probands has shown that other axis II personality disorders are as likely as or more likely than borderline personality disorder to be associated with depression (8, 9). Shea et al. (8) found that borderline personality disorder was relatively infrequent (2% to 8%) in a sample of depressed outpatients, whereas other axis II disorders (notably obsessive-compulsive, avoidant, and dependent personality disorders) were much more common.

These reports weaken support for hypotheses I and II, and although still consistent with hypothesis IV, they give surprisingly strong support to hypothesis III, i.e., that depressive disorder and borderline personality disorder are unrelated (table 2).

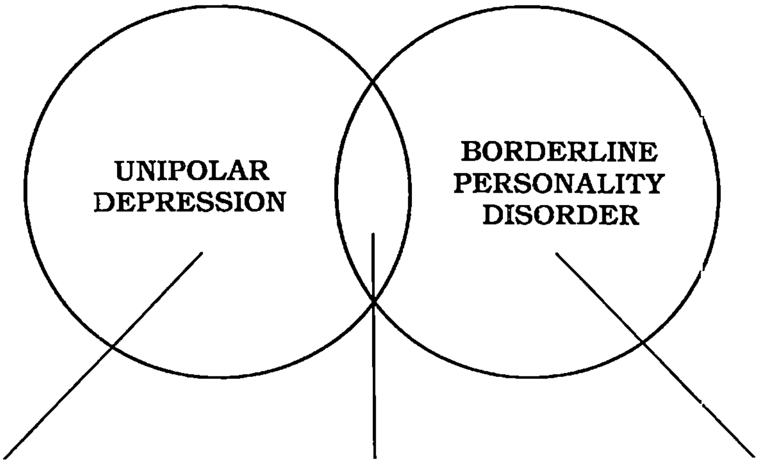
## PHENOMENOLOGY

An important issue noted in 1985 (table 1) is whether and how the depressive experiences of borderline patients differ from those of nonborderline patients. This issue is complicated by the likelihood that classic major depression is a heterogeneous, rather than a homogeneous, concept; similarly, as will be noted later in this review, the depressive experiences of borderline patients are also likely to be heterogeneous in nature. Despite these limitations, considerable research has been done in this area and has delineated, with some consistency, differences in the quality of depression in borderline and nonborderline patients.

Westen et al. (unpublished data) have recently shown that borderline patients frequently experience chronic emptiness, which is uncommon in nonborderline depressed patients (figure 1). It has been postulated that emptiness reflects a residual effect of a basic failure of early attachment (10) or a residual effect of unexpressed rage (11). Emptiness is the borderline feature least likely to resolve when behavioral markers (e.g., self-mutilation or substance abuse) of this disorder do (12; Perry, unpublished data), and its absence in patients who meet criteria for borderline personality disorder predicts a course more similar to that of affective disorder (2).

As first noted by Grinker et al. (13), the depression of

**FIGURE 1. Shared and Unshared Characteristics of Unipolar Depression and Borderline Personality Disorder**



Guilty, remorseful
Withdrawn/agitated
Suicidality (without gestures)
Stable relationships
Concerned with defeat, failures
Welcomes caregiving (with history of independence)

Depressed affect: early onset, sustained
Worthlessness/hopelessness
Object hunger
Dependency
Fragile self-esteem

Empty, lonely
Angry/needy
Repeated suicidal gestures
Demanding hostile-dependent relationships
Concerned with interpersonal loss, separation
Illusory self-sufficiency (with history of dependency)

borderline patients is also distinguished from that of nonborderline depressed patients by chronic feelings of loneliness (Westen et al., unpublished data). This loneliness, in turn, reflects the basically interpersonal source of borderline patients' depression and is associated with a long-standing and deeply felt sense of alienation and unfulfilled yearnings for close attachments. In contrast, nonborderline depressed patients are more likely to withdraw from others, and although they may welcome supportive attachments, they rarely report long-standing loneliness.

From another perspective, Perry and Cooper (5) distinguish borderline patients' action and splitting defenses from the narcissistic defenses used by patients with affective disorders. This is in line with a third distinction identified by the 1985 paper's psychoanalytic sources, namely, that borderline patients, unlike most depressed patients, typically have a long-standing sense of rage that, when consciously experienced, is harshly turned upon themselves in a way that often begets self-destructive impulses and acts. This is distinct from the ongoing erosion of confidence and self-esteem typical of nonborderline depressed patients, who tend to be burdened by an overly self-critical nature and are often "egged on" by perfectionistic goals to which they aspire and always fall short.

These distinctive features of the depressive experiences of borderline patients can be linked to efforts to identify psychological subtypes among depressed patients. Several investigators (14–16) have independently divided the psychological features of depressed patients into two subtypes: the *dependent* subtype, in which patients are lonely, rejected, yearning, and self-destructive, and the *self-critical* (or autonomous) subtype, in which patients are agitated, defeated, and withdrawn. Clearly, borderline patients would have the former, i.e., dependent, type of depression and would be expected to have depressive reactions in response to interpersonal loss or rejection. Of note, Frank et al. (17) concluded that it is such "interpersonally based" dependent types of depressed patients who are less responsive to medications; this is consistent with results of studies of pharmacotherapy for borderline personality disorder, as noted later in this review. Accordingly, Frank et al. suggest that the amounts of biological versus personality disturbance in depressed patients are inversely correlated.

Deserving mention is hysteroid dysphoria, an atypical form of depression that overlaps considerably with borderline personality disorder (18). One of its hallmarks—depressive reactions in response to interpersonal rejection—is also a feature of the previously mentioned borderline personality disorder-like dependent subtype of depression. Soloff (19) has demonstrated that hysteroid dysphoria is the predominant affective pattern in a sample of borderline patients, who, nonetheless, may also experience this pattern in combination with major depressive episodes. Both patients with hysteroid dysphoria and borderline personality disorder (see discussion later in this review) may respond preferentially to monoamine oxidase inhibitors (MAOIs) (18, 20).

Thus, although hysteroid dysphoria has questionable syndromal validity (21), it may help to capture the distinctive aspects of the depressive experience of borderline patients. This evidence highlights the importance of assessing and differentiating hysteroid dysphoric and classic depressive symptoms in future research on borderline personality disorder and depression.

Although the kind of clinical observations identified in figure 1 are generally not considered to constitute scientific evidence, as noted, those on borderline emptiness and loneliness have now been empirically substantiated. This is congruent with other empirical evidence demonstrating that the depressive experiences of patients with and without borderline personality disorder are often distinct. As illustrated in table 2, these findings add support to hypotheses II and III. Worth mentioning here is an additional hypothesis that avoids etiologic speculation and instead proposes that a personality type, such as borderline personality disorder, can *modify* the symptomatic expression of depression or affect more generally. As such, it could be speculated that the depressive experience of borderline patients differs from that of patients with major depression alone because their personality distorts the expression and experience of affect. Although this view is consistent with the evidence on phenomenology, it is not pursued because it is not supported by the other evidence presented in this review.

## FAMILY PREVALENCE

At the time of the 1985 review, all six of the existing family history studies had documented a higher-than-expected prevalence of affective disorder in the first-degree relatives of patients with borderline personality disorder. These reports were a cornerstone for theories linking borderline personality disorder and affective disorder (table 1). However, that interpretation now appears to be inaccurate. Both Pope et al. (22) and Zanarini et al. (23) have subdivided their patients with borderline personality disorder into those with or without concurrent affective disorder and have examined the effect on familial aggregation. These analyses reveal that the higher frequency of affective disorder in the relatives of patients with borderline personality disorder could be accounted for by concurrent affective disorder in the probands.

The earlier review of family history studies was also handicapped by the absence of similar data from patients without borderline personality disorder. If relatives of patients with other personality disorders have similarly high rates of affective disorder, this would argue for a nonspecific relationship between borderline personality disorder and affective disorder. Such a finding would be consistent with the reasonable assumption that the presence of affectively disturbed relatives may encourage the development of various types of personality disorders and other psychopathology in probands, or vice versa, i.e., that the presence of a personality disorder in probands may encourage the development of affective disorders in relatives. Zanarini et al. (23) found that patients with various types of personality disorder who were also dysthymic had more relatives with affective disorder than did patients with personality disorders who were not dysthymic. This was equally true for the borderline sample as for those with other personality disorders. The only other family history studies that have compared borderline probands to patients with another type of personality disorder involve schizotypal probands. Here the findings are mixed. In two studies, the relatives of borderline patients had no more affective disorder than did the relatives of schizotypal patients (24, 25). Baron et al. (26), however, found more depression in the relatives of their borderline cohort. Interpretation of this finding is complicated by Baron et al.'s use of nonclinical samples and the fact that only two members of their sample with borderline personality disorder met *DSM-III* criteria; in addition, the known familial relationship between schizotypal personality disorder and schizophrenia may have artifactually lowered the prevalence of affective disorder in the relatives. The facts preclude an interpretation that relates borderline personality disorder to affective disorder. In sum, these studies of probands without borderline personality disorder further undermine the claims of hypotheses I and II.

Not surprisingly, a series of studies has shown that probands with borderline personality disorder have familial aggregation of other types of psychopathology uncommonly found in relatives of probands with affective disorders. Namely, these studies document the far greater frequencies of borderline personality disorder, substance abuse, and antisocial behavior in relatives of probands with borderline personality disorder (23, 24, 27–29).

Recently, the first study examining the aggregation of all personality disorders in the relatives of depressed probands was reported. Coryell and Zimmerman (30) report that borderline personality disorder is not unusually prevalent in these relatives. When the depression was subtyped, nonendogenous depression in probands was associated with a higher prevalence of all dramatic-cluster personality disorders (not just borderline personality disorder) in relatives. Notably, proband bipolarity was associated with the anxious cluster rather than borderline personality disorder. Since evidence for a biogenetic etiology is stronger for bipolar disorder than for other types of affective disorder, this finding further refutes theories of a biogenetic linkage between borderline personality disorder and affective disorders. This is in accord with the findings from family history studies that used probands with borderline personality disorder and failed to show a relationship between it and bipolarity (22–24, 27). The one exception has been Akiskal et al. (28), who found a higher frequency of bipolar disorder in the relatives of borderline probands. Interpretation of this exception is difficult, however, given the fact that affective disorders (including bipolar variants) were present in 45% of the borderline sample but were not controlled for.

In sum, these studies show that the higher prevalence of affective disorder in relatives of patients with personality disorder is linked to the presence of affective disorder in the probands and thus, perhaps, not to the presence of personality disorder at all. In addition, affective disturbance in relatives is as common in other personality disorders as in borderline personality disorder and is certainly not specific to borderline personality disorder. Conversely, borderline personality disorder is not unusually prevalent in the relatives of depressed probands. The absence in most studies of any relationship between borderline personality disorder and cyclothymic or bipolar disorder underscores the fact that even a possible nonspecific linkage between borderline personality disorder and affective disorder is unlikely to be biogenetic in nature.

In general, the evidence from family history studies using standardized diagnostic assessments contradicts the theory that affective dysregulation is the core psychopathology of borderline patients or that biogenetic linkage to affective disorders accounts for the depressive or labile features of these patients (hypothesis I). Similarly, these data weaken the evidence for even a nonspecific linkage between the two disorders (hypothesis IV) and are instead most consistent with hypothesis III, i.e., the disorders are unrelated (table 2).

## MEDICATION RESPONSE

Since 1985, pharmacologic research has further eroded hypothesis I while offering complicated support for the other three hypotheses. The only double-blind, placebo-controlled trial of a tricyclic antidepressant (amytriptyline, N=90) showed that borderline patients had more antidepressant response to this medication than they did to placebo (31, 32). Yet the same study clearly differentiated their response to adequate dosage of tricyclics from that of patients with major depression: 1) haloperidol had equivalent antidepressant efficacy, 2) the presence of concurrent major depression did not predict response, and 3) many patients paradoxically became significantly worse, with an increase in impulsive, assaultive, and suicidal behavior (33).

Borderline patients appear to respond more favorably to MAOIs. Cowdry and Gardner (34, 35), in a placebo-controlled crossover study of four medications, found that the MAOI tranylcypromine produced the greatest improvement in depressive symptoms. However, improvement in depressive symptoms also occurred with a phenothiazine and—to a lesser extent—carbamazepine, and it was not predicted by a personal or family history of classic affective disorder (including major depression). The fact that Cowdry and Gardner's patients with borderline personality disorder also met criteria for hysteroid dysphoria may at least partly explain the success of MAOIs in this group. These findings, like those of Soloff (19), indicate that the affective symptoms of borderline personality disorder are different from those of classic major depression.

In the same study, Cowdry and Gardner also found that the anticonvulsant carbamazepine, which reduces affective dysregulation in bipolar disorder, decreased behavioral dyscontrol significantly more than affective symptoms and that improvement in these two domains was not highly correlated. The authors postulated (35, 36) that for these and other reasons, carbamazepine's effect on behavioral dyscontrol is independent of its effects on mood in borderline personality disorder. They similarly stated that although borderline personality disorder is sometimes viewed as a subaffective disorder (hypothesis I), the "pattern of mood and the prominence of behavioral dyscontrol suggest a mechanism different from that underlying the classical affective disorders" (hypothesis III).

Two small (N=5 [37], N=12 [38]) open trials recently assessed the efficacy of the antidepressant fluoxetine in borderline personality disorder. Although the fact that fluoxetine improved depressive symptoms would seem to give some support to hypothesis I, in both studies the investigators reached other conclusions. The fact that fluoxetine's effectiveness was not enhanced by concurrent major depression and the more impressive improvements seen in the area of impulse control led the investigators to conclude that effects were primarily behavioral, not mood regulatory. As such, these results do not inform the competing claims of the hypotheses.

The first, albeit preliminary, study of lithium in borderline personality disorder (39) found no significant differences between lithium and placebo or desipramine on depressive symptoms, although lithium showed some superiority over placebo on symptoms of impulse dyscontrol (39). The authors concluded that these findings are congruent with other reports of the relative lack of efficacy of tricyclics in borderline personality disorder, and they speculated that lithium's modest efficacy may reflect an effect on impulsivity and aggressivity—as has been reported in other nonmood disorders (40). These results thus seem to diminish support for hypothesis I while giving some support to hypothesis III and may, like the fluoxetine and carbamazepine studies, implicate the importance of impulse—rather than affective—dysregulation in borderline personality disorder.

Overall, response to antidepressant medications tends to be less predictable, uniform, and pronounced in borderline patients than in depressed nonborderline patients (41). In addition, the affective symptoms of borderline patients may respond as well to antipsychotics as to antidepressants. These findings further erode the plausibility of hypothesis I and, to a lesser extent, hypothesis IV. They are most consistent with hypotheses II and III. This conclusion does not imply that antidepressants do not have a role in the treatment of borderline personality disorder, but rather that their effect is not likely to be as specific or profound as in uncomplicated depressions.

## STUDIES OF BIOLOGICAL MARKERS

In the 1985 review, studies of proposed biological markers for depression (dexamethasone suppression test [DST], thyrotropin-releasing hormone [TRH] stimulation test, and sleep EEG) did not clearly favor any of the four hypotheses. This largely reflected methodological shortcomings—in particular, the high concurrence of borderline personality disorder and major depression in study populations. Since then, methodological progress and studies of other markers have allowed some clarification of the interface between borderline personality disorder and depression.

Most recent studies of the DST have demonstrated normal results for most borderline patients (42–44); in those with an abnormal response, a coexisting major depression may have accounted for the nonsuppression. Even in this group, rates of nonsuppression tended to be lower than the usual rates in patients with major depression alone. Similarly, one study found a low rate of thyroid-stimulating hormone blunting in borderline patients regardless of the presence of depression (43). Newer marker studies, which have measured platelet MAO levels and in vitro red blood cell lithium ratios in borderline patients, have also demonstrated abnormalities that could be explained by coexisting axis I disorders (44). In sum, the findings from these marker studies do not support the concept that borderline personality disorder is an affective variant (hypothesis I).

EEG sleep studies indicate that while many borderline patients have some of the REM abnormalities characteristic of major depressive disorder (shortened REM latency and higher REM density), these are most pronounced and consistently found in those patients with past or present mood disorder (44–47). In the study of Lahmeyer et al. (44), which most systematically and thoroughly assessed a wide range of comorbid axis I diagnoses, borderline patients with coexisting major depression had either normal or abnormal REM latency and density, but borderline patients without major depression had clearly normal findings.

A study by Kutcher et al. (48) sheds new light on the interface between borderline personality disorder and depression. This group assessed the auditory P300 (P3) evoked potential, which is abnormal in schizophrenic but not depressed patients. They found that potentials of borderline personality disorder patients with and without concurrent major depression were significantly different from those with major depressive disorder alone. In fact, abnormalities in patients with borderline personality disorder (even those without coexisting schizotypal personality disorder) were similar to those in schizophrenic patients. These results may simply indicate that borderline patients and schizophrenic patients share a common auditory information processing dysfunction. However, Kutcher et al. went further by concluding that their results support a linkage between borderline personality disorder and schizophrenia, but not between borderline personality disorder and depression.

More recent laboratory investigations of biological abnormalities in borderline personality disorder have focused on the neurotransmitter serotonin—in particular, lower serotonergic function. Lower CSF concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) and a blunted serum prolactin response to challenge with fenfluramine (a serotonin releaser and uptake inhibitor) have been correlated with histories of suicide attempts and impulsive aggression (49, 50). In particular, prolactin response has been found to be lower in patients with borderline personality disorder than in patients with nonborderline personality disorders or major depression or in healthy control subjects and was associated with the borderline patients' greater impulsive/aggressive, rather than depressive, symptoms (50). Because these results, together with the studies on fluoxetine and lithium noted earlier, suggest the importance of impulse dysregulation, as opposed to affective dysregulation, in borderline personality disorder, they give some tentative support to hypothesis III. However, serotonin dysregulation is not likely to be specific to borderline personality disorder, since a low CSF 5-HIAA and a blunted prolactin response to fenfluramine have been reported in other psychiatric disorders, including major depression.

In a recent and comprehensive review of biological marker studies in borderline patients, Lahmeyer et al. (47) noted the methodological shortcomings of most of these studies. Nonetheless, they believe that the findings are sufficiently consistent to conclude that "biologic marker studies argue against a close biologic association between BPD and depression." We agree, and, more specifically, we conclude that these results disconfirm the concept that borderline personality disorder is a form of affective disorder (hypothesis I) and instead give their strongest support to hypothesis III (table 2).

## PATHOGENESIS

Because at the time of the 1985 review only one study had compared the environmental background of depressed and borderline patients, this area was not considered sufficiently researched to be included. That study (51) found that pathological sensitivity to separation experiences was twice as common among depressed borderline patients as among patients with major depression. It also found that the borderline personality disorder cohort's significantly higher rate of early parental loss (before age 6) was due largely to the father's absence because of divorce or death. The fathers who remained tended to be underinvolved with their children. Subsequently, Akiskal et al. (28) found that borderline patients were significantly more likely than control subjects with affective disorders to have a history of childhood object loss as well as parental assortative mating (i.e., both parents had psychiatric illness), the latter apparently leading to a troubled home environment with subsequent frequent separations, foster care, or adoption. Links et al. (52) also found that although borderline patients and patients with affective disorders share high rates of early parental loss or separation, borderline patients are more likely to experience these losses in the context of an inadequate other parent, i.e., biparental psychopathology. Patients with affective disorders are less likely to experience early loss or separation in the context of inadequate alternative sources of support or more generally inadequate parenting.

Ogata et al. (53) have also compared the family backgrounds of borderline and depressed samples. Although both disorders arise in families that do little to promote independence, in other ways the family backgrounds sharply differ. Families of borderline patients are far less organized, have more hostile conflict, and are less cohesive than families of depressed patients. Thus, in several major respects, the family background of depressed patients is far less pathological.

Recent investigators (54–57) have documented a much higher frequency of sexual and physical abuse in the family backgrounds of patients who become borderline than in patients who develop depression. This finding, combined with the findings of more antisocial behavior and substance abuse in the family pedigrees of borderline patients noted earlier, has seeded a new theory that places the core psychopathology of borderline personality disorder in the sphere of impulse dyscontrol rather than affective dysregulation.

The growing evidence on pathogenesis suggests some similarities between borderline personality disorder and depression but, more significantly, highlights some important differences. The evidence supports theories of heavy environmental loading in the causation of borderline personality disorder and, in contrast, of relatively heavier constitutional loading in the origin of usual depressive disorder. Although this evidence is consistent with hypotheses I, II, and IV, as shown in table 2, this new evidence also weakens the claims of all three because it suggests some specificity to the different origins of these syndromes. The evidence for different and specific developmental pathways lends support primarily to hypothesis III.

## SUMMARY AND CONCLUSIONS

It can now be clearly stated that hypothesis I (i.e., that affective dysregulation is the primary problem for patients with the borderline syndrome) is not viable. It is still unclear whether, as suggested by hypothesis II, borderline personality can produce the diagnosable affective disorders that commonly co-occur in these patients. Even if it can, this relationship is nonspecific, i.e., although borderline patients often meet criteria for axis I depressive or dysthymic disorders, so do patients with other personality disorders.

Ironically, although on the basis of his study of borderline patients Akiskal has been an advocate for hypothesis I (45), his work on dysthymic patients (58) seems to give some support to hypothesis II. In that work, on the basis of multiple external validators, Akiskal empirically subdivided patients with chronic, early-onset "characterologic" depressions into affective and nonaffective subtypes (58). Patients in the affective subtype, which he believes is related primarily to bipolar disorder, are characterized by a family history of affective illness, unremarkable developmental history, responsiveness to antidepressants and lithium, shortened REM latency, and Schneiderian depressive personality traits. This subtype may correspond to the concept of the depressive personality (59). In contrast, Akiskal's nonaffective subtype of characterologic depression ("character-spectrum disorder") clearly differs from affective disorder on these measures and echoes the borderline personality disorder characteristics mentioned in this review: family history of sociopathy and alcoholism but not affective disorder, childhood loss and separation, lack of response to antidepressants and lithium, normal REM latency, substance abuse, and "unstable" character traits (notably including borderline features). Akiskal's conclusion that this group may develop dysphorias secondary to the underlying nonaffective character pathology is more in keeping with hypothesis II than hypothesis I. His advocacy of hypothesis I derives from his study of a borderline sample that had more primary affective disorder (largely bipolar II disorder, cyclothymia, and dysthymia) than character spectrum disorder (28). However, that conclusion must be considered with caution, given the uncertain standards for diagnosing "subaffective" disorders and the finding by others, noted earlier, that other personality disorders have as much or more comorbidity with affective disorder.

Current evidence, as reviewed in this paper, seems to best support hypothesis III, i.e., that the two disorders coexist but are otherwise unrelated. This is suggested by the qualitatively different (e.g., more empty and lonely) nature of the borderline patient's depression, which appears to be more developmentally and interpersonally based. It is also strongly supported by the family history data, which upon closer and more refined examination reveal distinct patterns of familial transmission. Borderline depressions are also less apt to respond to antidepressant pharmacotherapies, suggesting a different neurophysiologic substrate. It follows from these differences in phenomenology, pathogenesis, family history, and therapeutic responsiveness, as well as from the biological marker data, that our diagnostic system should distinguish between the dysphorias commonly found in borderline patients and prototypic axis I depressions.

This review has touched on evidence that suggests what borderline personality disorder's primary neurophysiologic substrate may consist of. The possible efficacy of serotonergic medications and an abnormal response to fenfluramine challenge suggest that central serotonin function may be low in borderline patients. Furthermore, the finding that low serotonin function is associated with impulsive aggressive behavior—in particular, irritability and assaultiveness—in borderline personality disorder combines with the familial linkage of borderline personality disorder to other impulse/action disorders to raise the question of whether impulse dysregulation, as opposed to affective dysregulation, is primary in this disorder.

Although the bulk of the data best supports hypothesis III, it does not rule out hypothesis IV—i.e., the possibility that the factors leading to depressive disorders and borderline personality interact and overlap in complex ways. Both disorders are more likely to occur in families that have affectively disturbed members and that discourage independence; this, along with earlier findings on the psychodynamics and course of borderline personality disorder, retains support for hypothesis IV. Moreover, hypothesis III has some conceptual and practical hazards. The conceptual hazard is that the etiology of both disorders is probably best understood in terms of a polygenic multifactorial model (see Gunderson and Zanarini [60] for borderline personality disorder and Whybrow et al. [61] for depression), which raises the possibility of some shared etiologic sources. If so, this might promote an incomplete separation—i.e., a "fuzzy border"—between them. Certainly we, like Akiskal, feel strongly committed to the concept of a spectrum of depressive disorders—from the more discrete episodic disorders on axis I to the enduring character types properly identified alongside axis II disorders. The practical hazard of hypothesis III is that patients with the borderline syndrome sometimes respond partially and occasionally respond dramatically to antidepressants, suggesting that clinicians should not rule out use of this treatment.

It is worth noting the problems that surround the development of diagnostic criteria that are not anchored by multiple external validators. Earlier investigators who concluded from comorbidity and family history data alone that the borderline patient's core psychopathology derives from a basic affective dysregulation, as suggested by hypothesis I (45, 62, 63), might feel that criteria for borderline personality disorder should reflect the centrality of affect as, in fact, four of the *DSM-III-R* criteria do. This contrasts with other conceptualizations of the disorder's core psychopathology, which would most heavily weigh problems of impulse dysregulation (34, 50, 64), interpersonal relations (65, 66), and neurologic deficits (67). Any of these conceptualizations of borderline personality disorder would be more consistent with hypothesis III and would shift interface questions—and the diagnostic criteria set—away from depression and toward other disorders. These questions have been considered by the *DSM-IV* axis II work group and have given rise to proposed modifications (68). One proposed modification has been to alter criterion 3 from affective instability to affective reactivity—thereby linking it to interpersonal crises and diminishing the suggestion of autonomous mood shifts. A second modification drops boredom and highlights emptiness, reflecting their discriminatory effectiveness. The most basic modification proposed is in the essential feature, which now includes impulse dysregulation alongside unstable affect, self-image, and relationships. This review raises the question as to whether, even with these changes, affective dysregulation is not still misleadingly overrepresented.

The clinical implications of this review are several. First, clinicians should not expect all patients with depressive problems to have an affective illness. Second, the interface between depression and personality disorders can best be evaluated by a longitudinal history of personality traits and their association with depressed states. And, finally, for most depressed borderline patients, long-term multimodal strategies remain central to therapeutic planning.

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# Magnetic Resonance Spectroscopy in Psychiatry: Potential, Pitfalls, and Promise

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*Magnetic resonance spectroscopy (MRS) is a novel noninvasive approach to measuring important metabolites in living tissue. Its application to psychiatry is just beginning. In vivo MRS with $^{31}P$ provides important information on brain phospholipid metabolism and energy production. In vivo $^{13}C$ and $^{1}H$ MRS can reveal information about carbohydrate, protein, and amino acid metabolism. In vivo $^{7}Li$ and $^{19}F$ MRS can be used to study the pharmacology of lithium and fluorinated psychopharmacological agents. MRS with $^{23}Na$ can yield information about electrolyte balance. The limitations of in vivo MRS include poor sensitivity, poor resolution, and the fact that only highly mobile atomic nuclei can be detected. Future clinical application of MRS will benefit from improvements in the technology of localization, use of spectroscopy contrast agents, stronger magnets, and the merging of MRS and imaging technology.*

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In his presidential address to the Royal Society in 1885, T.H. Huxley said, "What an enormous evolution would be made in biology, if physics or chemistry could supply the physiologist with a means of making out the molecular structure of living tissues comparable to that which the spectroscope affords to the inquirer into the nature of the heavenly bodies" (cited by Radda [1]). Magnetic resonance spectroscopy (MRS), the topic of this review, has raised hopes that this prediction will soon be realized.

The last two decades have witnessed an exponential increase in the application of brain imaging techniques, such as computerized tomography (CT) and magnetic resonance imaging (MRI), in psychiatric research. Emphasis has, however, recently shifted from anatomical to "physiological" techniques, such as MRS, a noninvasive in vivo approach to measuring important metabolites in living tissues. We describe the history of MRS, its basic physical principles, the available techniques, the chemical insights made available, and potential applications to psychiatry. Physics-related details and work related to organs other than the brain are well reviewed elsewhere (2–8).

## HISTORY

In 1946 Purcell et al. (9), using a discarded generator from the Boston elevated railway, first demonstrated "nuclear magnetic resonance" (NMR) and discovered that the magnetic dipoles of molecules in matter resonate in response to an externally applied field. At the same time Bloch et al. (10), using an electromagnet borrowed from a physics lecture theater at Stanford University, observed the same phenomenon. Bloch et al. noted that nuclei resonating to an external magnetic field induce an electromotive force in a surrounding recording coil. The importance of this discovery was recognized by the award of the Nobel Prize for physics to Bloch and Purcell in 1952 (11).

The lineage of the first biological applications can be traced to the curiosity of the originators of NMR. Bloch inserted his finger into the radio frequency (RF) coil of his spectrometer and obtained a strong NMR signal. In 1948 Purcell inserted his head into the Harvard cyclotron with an RF coil surrounding his head and recorded signals generated by his dental fillings. Further biological applications followed the development of high-field, high-resolution magnets and of Fourier transformation software. In 1973 Moon and Richards (12) conducted $^{31}P$ NMR studies of intact erythrocytes. Simultaneously Hoult et al. (13) recorded a $^{31}P$ NMR spectrum from an intact freshly excised muscle from a rat's leg. After superconducting magnets with large bores became available, human limbs became objects of study; because of limitations on magnet bore size, infants' heads were studied before the technique was used to study adult brains (14).

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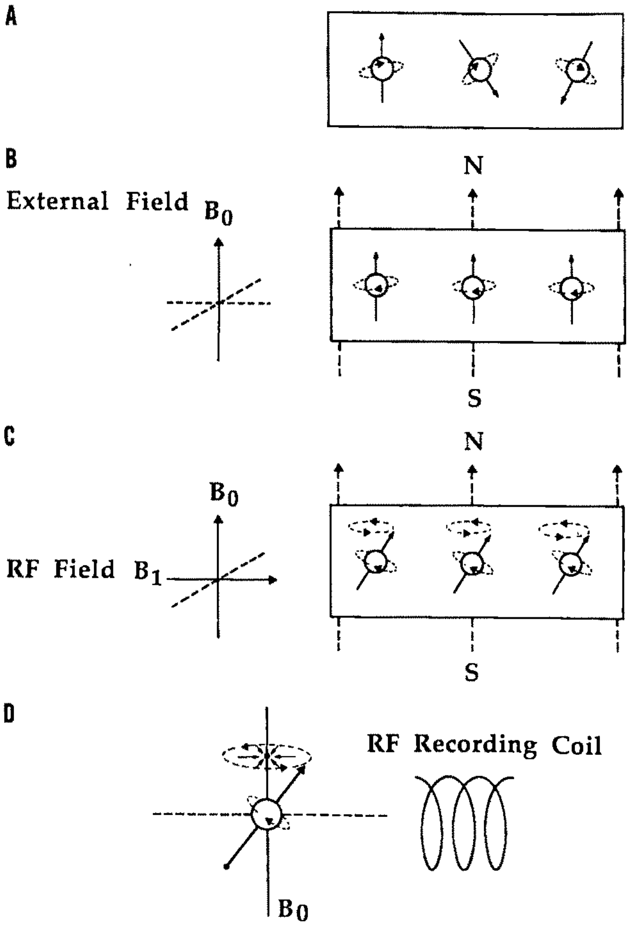
**FIGURE 1. Alignment of Atomic Nuclei With No External Magnetic Field (A), With External Magnetic Field (B), With Additional Radio Frequency (RF) Field (C), and After Removal of RF Field (D)**[a]



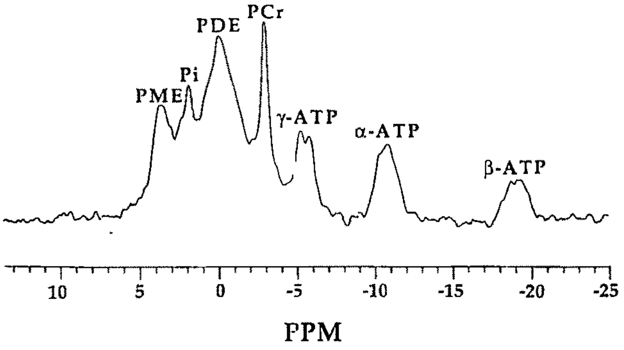
[a] A) Matter shown here is composed of multiple nuclei. As these nuclei are charged and have a net spin (spin shown by dotted arrows), they act like tiny magnetic dipoles (represented by solid arrow). At rest all dipoles are arranged randomly. B) On application of an external field, $B_0$, the magnetic dipoles (solid arrows) arrange themselves along the direction of the external field (broken arrows). C) On application of an additional RF field, $B_1$, the dipoles already aligned along $B_0$ now start precessing around axis $B_0$. D) On removal of the RF field, the precessing dipole returns to alignment along axis $B_0$. This process, called "relaxation," is characterized by $T_1$ and $T_2$ (see text) and induces an electromotive force in the recording coil.

As compared with MRI, which has rapidly advanced (15), MRS seems to have lagged behind, perhaps because of more stringent technical requirements. Presently MRS is studied 1) in research laboratories using high-resolution magnets which do not have the capacity for human in vivo studies and 2) in NMR imaging centers, where the same basic instrument is used for MRI and MRS.

## PRINCIPLES OF MAGNETIC RESONANCE

An atom has a positively charged core made of neutrons and protons and a shell of negatively charged electrons. The core of $^{1}$H contains only one proton, and $^{7}$Li has three protons and four neutrons. Each particle spins about an axis, generating a small magnetic field (figure 1A). Each particle with a charge and a spin can be visualized as a small bar magnet. However, not every atom has a spin, e.g., $^{1}$H with one proton has a spin, but in $^{4}$He two protons and two neutrons cancel each other's spin. Only atoms with net spins lend themselves to NMR, and thus $^{1}$H, $^{13}$C, $^{19}$F, $^{23}$Na, and $^{31}$P have been atoms of interest.

**FIGURE 2. $^{31}$P NMR Spectrum of Dorsolateral Prefrontal Cortex in a Healthy Human Volunteer**[a]

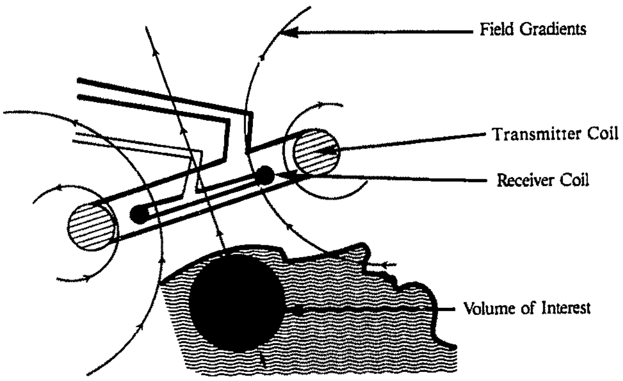


[a] PME=phosphomonoester, Pi=inorganic phosphate, PDE=phosphodiester, PCr=phosphocreatinine. The same element in different chemical compounds resonates at slightly different frequencies because of the magnetic fields of surrounding atoms; this effect is called the "chemical shift" and is described in units of parts per million (PPM) in relation to a central radio frequency.

In the absence of an external magnetic field, all atoms in matter are randomly aligned, so the total vectorial sum of all the magnets is zero. When an external magnetic field, $B_0$, is imposed, the tiny magnets line up along the direction of the magnetic field (figure 1B). In this state matter can be considered to be made up of multiple tops, all spinning about the axis of the external field (z axis). If another field, $B_1$, generated by an RF coil, is now applied, the spinning tops can be "tipped" in the x-y axis, thus being elevated to a higher state of energy; the nuclei that were initially spinning around the $B_0$ axis will start precessing around that axis in addition, like a top spinning about the spike (figure 1C).

In a given magnetic field, each distinct nuclear species resonates at a unique frequency, the Larmor frequency. This is derived by the equation $V_0=\gamma B_0/2\pi$, where $V_0$=resonating frequency (frequency of applied RF field), $\gamma$=gyromagnetic constant, $B_0$=externally applied static field. By using this equation it is found that in an external magnetic field of 2.35 T (1 T=$2.35\times10^4$ gauss) the resonating frequency for $^{1}$H is 100.00 MHz and that for $^{31}$P is 40.48 MHz (16). Thus, in a chemical mixture that contains $^{1}$H and $^{31}$P, one can selectively apply an RF field with a frequency of 100.00 MHz and resonate only $^{1}$H or apply an RF field with a frequency of 40.48 MHz and resonate only $^{31}$P. The former would be called "$^{1}$H MRS" and the latter "$^{31}$P MRS."

**FIGURE 3. Diagram of Surface Coil Used for MRS**



Once the RF field is removed, the resonating nuclei return to their original axes ("relaxation") (figure 1D). The change of orientation of these tops in the presence of the external magnetic field ($B_0$) induces a voltage signal in a recording coil around this material. However, not all the precessing tops return in synchrony, so the signal recorded varies with time as it decays. $T_1$ and $T_2$, relaxation times, are measures of the rate of decay of this signal. The component of the relaxation to the z axis is termed "longitudinal" or "spin-lattice" relaxation ($T_1$), and the relaxation in the transverse (x-y) direction is termed "spin-spin" relaxation ($T_2$).

The resonance frequency of a nucleus is also affected by the magnetic field of the surrounding atoms; this effect is called the "chemical shift" and is described in units of parts per million in relation to a central radio frequency. Thus, the same element in different chemical compounds resonates at slightly different frequencies, resulting in distinct MRS peaks. The areas under different peaks can represent the relative quantities of different metabolites. The phosphorus resonances from distinct phosphates in ATP can thus be detected separately by $^{31}P$ MRS (figure 2). To detect such minute changes in NMR frequency caused by the chemical shift, an extremely homogeneous external magnetic field is necessary. The sharpness of each peak, or line width, is determined by the homogeneity of the magnetic field; increasing the homogeneity ("shimming") helps in obtaining narrow line widths (7). To get an acceptable signal-to-noise ratio, the MR signal has to be averaged many times; thus, several minutes are needed to obtain a single MR spectrum. The signal-to-noise ratio is also affected by the rate at which the RF pulse is repeated (TR, or repetition time). When TR is shorter than $T_1$, saturation effects occur, resulting in a reduction in signal. Technically more detailed descriptions of the principles of NMR are available elsewhere (5–8, 16–18).

## TECHNIQUE OF MRS

The instrumentation for MRS, like that for MRI, requires a magnet, an RF transmitter coil, an RF receiver coil, and a computer. However, the following differences exist: 1) MRS needs a higher magnetic field homogeneity (1.5–2.5 T) to preserve information on the chemical shift, 2) a broad range of frequencies need to be generated to study nuclei with varying resonance frequencies, and 3) the source of the signal needs to be localized to a volume of interest. The use of a surface coil placed near the area of interest is the simplest way to acquire signals from a subject. Clinical applications of MRS have thus far mostly involved this technique (figure 3). A surface coil is commonly made of two concentric coils—a transmitter coil and a receiver coil. The region of interest is usually limited in depth to one coil radius (19). The main disadvantage of surface coils is that volume selection is confined to a region near the surface.

**TABLE 1. Isotopes With Nuclei That Can Be Detected by Magnetic Resonance Spectroscopy (MRS)**

| Isotope | Intrinsic Sensitivity[a] | Natural Abundance (%)[b] |
|---|---|---|
| $^{1}H$ | 100.00 | 99.98 |
| $^{13}C$ | 1.59 | 1.10 |
| $^{19}F$ | 83.40 | 100.00 |
| $^{23}Na$ | 9.24 | 100.00 |
| $^{31}P$ | 6.64 | 100.00 |
| $^{7}Li$ | 29.00 | 92.60 |

[a] Relative sensitivity to detection by MRS.
[b] Extent to which an isotope constitutes the element under natural conditions.

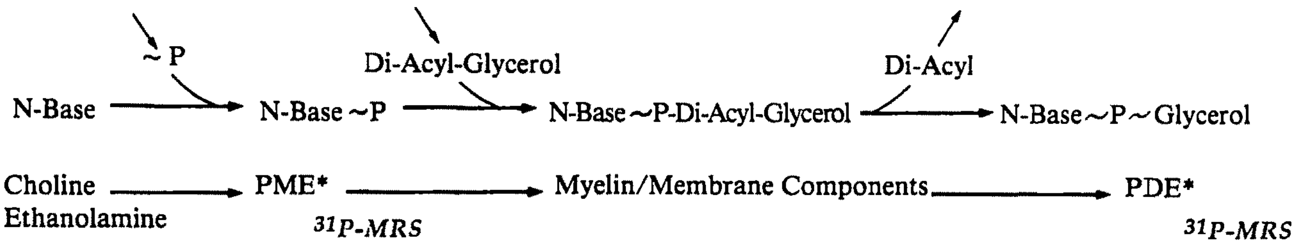
There are several other approaches to localization, none of which is unarguably superior. Most involve extensions of MRI techniques, i.e., using magnetic gradients that make the frequency vary with the distance, thus enabling spatial encoding of the MR signal. These include chemical-shift imaging (CSI) (18), depth-resolved surface coil spectroscopy (DRESS) (20), and image-selected in vivo spectroscopy (ISIS) (21). In CSI, one-, two-, or three-dimensional spectral information can be obtained by using a series of gradient fields. In DRESS, a plane parallel to the face of a surface coil is selectively excited, and this excitation provides spectral information about a disk-shaped volume. By using ISIS, a currently favored technique, the MRS signal can be localized to an axial "slab" of brain tissue at the level of the cerebral ventricles.

In addition, image-processing equipment is needed in MRS for visualization of the region of interest. Spectral display, measurements of peak areas, and calculation of chemical shift frequencies are carried out at a spectroscopy data processing workstation.

## WHAT MRS TELLS US ABOUT IN VIVO CHEMISTRY

For an element to be studied by MRS, it should lend itself to excitation by magnetic resonance, it should be present in a detectable concentration (table 1), and it should produce an acceptable signal-to-noise ratio. These conditions are met by $^{31}P$, $^{1}H$, $^{19}F$, $^{13}C$, $^{7}Li$, and

FIGURE 4. Major Intermediates in Phospholipid Metabolism[a]



[a]Intermediates marked * can be measured with $^{31}$P MRS. PME=phosphomonoester, PDE=phosphodiester, N-base=nitrogenous base.

$^{23}$Na, and by using these isotopes it has been possible to study various aspects of metabolism.

*Membrane Phospholipid Metabolism*

Phospholipids are integral constituents of cell membranes and are involved in the preservation of structure, ion conduction, signal transduction, and maintenance of concentration gradients. Phosphomonoesters (PMEs) are the precursors and phosphodiesters (PDEs) are the degradation products of membrane phospholipids (e.g., phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine) (figure 4) (22). By using $^{31}$P MRS to conduct in vivo and in vitro studies of extracts of frozen brain tissue, the concentrations of PMEs and PDEs and their ratios can be estimated; these measures reflect membrane turnover and may differ between health and disease states.

*High-Energy Phosphate Metabolism*

All life processes need energy, which is generated by metabolism of carbohydrates, lipids, and proteins in the Krebs cycle (figure 5). This energy is secured as ATP; any excess is stored as phosphocreatinine. ATP is used for polymeric biosynthesis, structural repair, ion conduction, muscle contraction, and nerve conduction. Energy is stored in the long term in the form of glycogen, carbohydrates, and long-chain fatty acids.

With $^{31}$P MRS one can glean information about bioenergetics by assessing the amounts of the $\alpha$-, $\beta$-, and $\gamma$-phosphate moieties of ATP, phosphocreatinine, and inorganic phosphate. Diseases associated with hypoxia, ischemia, anaerobic metabolism, and impaired energy utilization perturb the levels of ATP, phosphocreatinine, and inorganic phosphate. In the absence of oxygen, anaerobic metabolism proceeds (figure 5). Pyruvate, instead of entering the Krebs cycle, generates lactate and lowers pH. Lactic acid is "visible" with $^{1}$H MRS; $^{31}$P MRS, by measuring the acid-induced shift in the spectrum of inorganic phosphate, can determine the pH and, indirectly, the amount of lactate.

*Carbohydrate, Amino Acid, and Lipid Metabolism*

In vivo $^{13}$C MRS can be used to measure and identify triglycerides, glycogen, and fats. Further definition can be obtained in animals if a diet enriched in nonradioactive $^{13}$C-labeled glucose or $^{13}$C-labeled acetate is fed. The signal obtained from this dose of $^{13}$C can be used to study the way in which ingested nutrients are incorporated, stored, and metabolized.

MRS with $^{1}$H, even though most sensitive, is limited by the intense background signal from $^{1}$H in body water, which is 10,000 times as abundant as $^{1}$H from any other molecule, drowning all other signals. However, a computational technique is available to suppress the water resonance. $^{1}$H MRS of tissue extracts reveals identifiable resonances from amino acids, neurotransmitters, and their derivatives; metabolites related to energy production and use, such as glucose, phosphocreatine, creatine, lactate, and acetate; metabolites related to phospholipid metabolism, such as phosphocholine and phosphoethanolamine; and metabolites related to nucleotide metabolism, such as adenine, guanine, uracil, and cytosine (23).

*Electrolyte Balance*

Sodium, another element that lends itself to MRS, is largely extracellular. Injury, inflammation, edema, and tissue death cause a shift of sodium from outside to inside the cell. Using paramagnetic-shift reagents that are distributed exclusively outside the cell and shift the spectra from the extracellular $^{23}$Na signal, one can study the ratio of the $^{23}$Na inside and outside the cell (24). This technique may thus help in earlier identification of disease states affecting electrolyte balance.

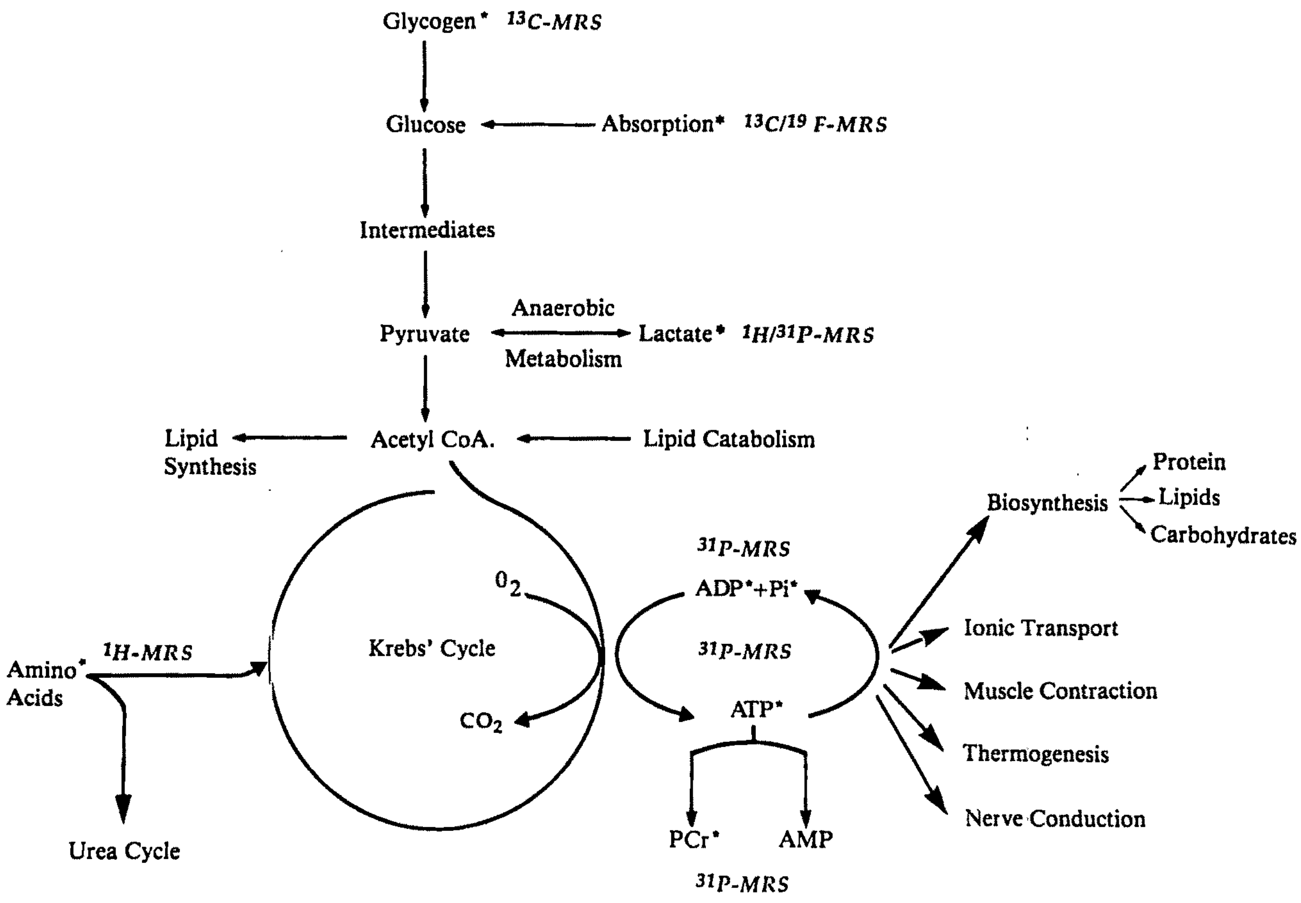
## CLINICAL APPLICATIONS

### *$^{31}$P MRS*

$^{31}$P MRS has been the most widely applied technique because 1) 100% of all phosphorus nuclei in the body are $^{31}$P nuclei, so no labeling is required, 2) the $^{31}$P nucleus provides sharp NMR signals for a variety of important phosphorus-containing compounds, and 3) $^{31}$P MRS analyses compare favorably with classic biochemical techniques without the need for tissue extraction (25).

An in vitro $^{31}$P MRS study of post-mortem brain ex-

**FIGURE 5. Metabolic and Energy-Releasing Pathways Essential to a Mammalian Cell**[a]



[a] Products marked * can be measured with MRS in vivo and in vitro. PCr=phosphocreatinine, Pi=inorganic phosphate.

tracts from patients with Alzheimer's disease (26) has shown that early in the disease PME levels are higher than those of nondiseased comparison subjects and that later PDE levels are higher than those of comparison subjects. PME levels were inversely related and PDE levels were positively related to the number of senile plaques. It was concluded that high PME levels occur early in Alzheimer's disease and that high PDE levels occur later, paralleling the appearance of senile plaques. In vivo $^{31}P$ MRS studies of patients with Alzheimer's disease (27) have shown high levels of PME and high ratios of PME to PDE in the temporoparietal regions and high levels of inorganic phosphate in the frontal and temporoparietal regions. Pettegrew et al. (28) carried out in vivo $^{31}P$ MRS studies of six patients with probable Alzheimer's disease and six age-matched elderly comparison subjects. Scores on the Mattis dementia scale were correlated negatively with PDE levels and positively with phosphocreatinine levels. The correlation between phosphocreatinine and Mattis score points to either less synthesis or more utilization of phosphocreatinine than normal early in the course of the disease. These in vivo $^{31}P$ MRS findings, if confirmed, could prove valuable in noninvasive monitoring of the biochemical substrate of primary degenerative dementias.

Brown et al. (27) showed that 10 patients with multi-infarct dementia had higher levels of phosphocreatinine and higher ratios of phosphocreatinine to inorganic phosphate than did patients with Alzheimer's disease or age-matched comparison subjects. This finding may reflect an impairment in energy mechanisms in multi-infarct dementia. The ratios of phosphocreatinine to inorganic phosphate accurately classified 100% of the patients with multi-infarct dementia and 92% of those with Alzheimer's disease. PME and inorganic phosphate levels also correctly classified all multi-infarct dementia patients and all but one patient with Alzheimer's disease. Thus, in vivo $^{31}P$ MRS measurements are potentially valuable in the differential diagnosis of Alzheimer's disease and multi-infarct dementia. Somewhat high levels of PDE were detected in deeper tissues, corresponding principally to white matter, in two patients with Binswanger's disease, a disease of small vessels in the brain (29).

Studies using $^{31}P$ have shown PME levels significantly higher than normal and PDE levels somewhat higher than normal in post-mortem brain extracts from patients with Huntington's disease (22). However, in vivo $^{31}P$ MRS carried out in a few such patients has revealed no significant abnormalities (5). The in vivo studies, however, did not focus on the same brain areas as the in vitro study, and it is known that the neuropathology varies from region to region.

$^{31}P$ MRS studies of newborn infants with congenital cerebral atrophy, propionic acidemia, arginosuccinic acidemia, and meningitis have revealed low ratios of phosphocreatinine to inorganic phosphorus and abnormalities in pH (14). Such abnormalities predicted poor outcome and subsequent neurological abnormalities (30).

Minshew et al. (31) recently compared the $^{31}P$ MRS profiles of eight nondemented adult patients with Down's syndrome (age=22–55 years, IQ=15–70) and eight age-matched normal-IQ comparison subjects. The patients with Down's syndrome had a significantly higher mean phosphocreatinine level and a significantly lower -ATP level; the PME and PDE levels were not significantly different.

Seizures are associated with profound abnormalities in cerebral metabolism, and $^{31}P$ MRS provides a method for monitoring such changes in vivo. Schnall et al. (32) used triple nuclear MRS in vivo ($^{1}H$, $^{31}P$, and $^{23}Na$) during various levels of seizure activity in cats. They demonstrated increased lactate levels and decreased phosphocreatinine levels during the seizures and an intracellular shift of the sodium ion pool. Weiner et al. (33) have shown an increase in pH and inorganic phosphate in localized seizure foci in a patient with refractory complex partial seizures. The causal relationship of these MRS findings to epilepsy is unclear.

There is evidence suggesting that schizophrenia is associated with abnormalities in membrane phospholipids in erythrocytes (34), and this has stimulated studies of brain membrane composition with $^{31}P$ MRS. Such studies of the prefrontal lobe have been carried out in neuroleptic-naive first-episode schizophrenic patients, who were compared with age- and sex-matched comparison subjects (35, 36). The following metabolic differences were observed in the schizophrenic patients: 1) lower PME levels, 2) higher PDE levels, 3) higher -ATP levels, and 4) lower levels of inorganic phosphate. The PME and PDE results suggest less synthesis and more breakdown of membrane phospholipids than in the comparison subjects. The ATP and inorganic phosphate findings suggest hypoactivity of the prefrontal cortex. O'Callaghan et al. (37) carried out $^{31}P$ MRS of the left temporal lobe of 12 schizophrenic patients and nine normal subjects. No significant differences emerged, except for a higher pH in the schizophrenic patients. However, the normal subjects were older than the schizophrenic patients, and the effects of neuroleptics could not be excluded.

Pettegrew et al. (38) have demonstrated that autistic patients have abnormally low levels of phosphocreatinine and of -ATP, suggesting abnormalities in brain high-energy phosphate metabolism. These findings are distinct from those for schizophrenia, a condition for which autism is frequently mistaken.

Membrane phospholipid and high-energy phosphate metabolism are influenced considerably by brain development and aging, as demonstrated by high-resolution $^{31}P$ MRS of rat brain extracts (22). Phosphocreatinine and PDE levels increase and PME levels decrease during dendritic proliferation and then remain stable until senescence. Similar findings have now been demonstrated by in vivo $^{31}P$ MRS in normal human volunteers aged 8–86 years (Pettegrew et al., unpublished observations).

In vitro MRS studies can be used to examine ethanol-induced membrane perturbation and to measure the partitioning of ethanol across the membrane (39). A $^{1}H$ MRS study showed that alcohol administration resulted in increased CNS membrane fluidity and water content of tissues in rats (40). To our knowledge, there have been no in vivo MRS studies of the effects of alcohol on the human brain.

$^{31}P$ MRS could prove valuable in studying the CNS effects of drugs because it is noninvasive and can be performed before and after administration of a pharmacological agent. By using $^{31}P$ MRS, it is possible to detect accumulation of PMEs after administration of lithium to cats in therapeutically meaningful doses (41). It is an intriguing possibility that such effects could parallel lithium's therapeutic effects. MRS studies with $^{31}P$ have shown that calcium antagonists prevent the rapid decrease of ATP and phosphocreatinine in rat brains during ischemia, indicating a possible protective effect (42).

MRS using $^{31}P$ also provides a way to noninvasively monitor second-messenger-mediated events in the brains of living subjects. It has been used to detect the muscarinic-agonist-induced accumulation of PMEs (such as inositol phosphate) in cats (43). Longitudinal and drug-related monitoring of changes in phospholipid metabolism could be of enormous value in the study and treatment of neuropsychiatric disorders.

## *$^{19}F$ MRS*

$^{19}F$ has an intrinsic sensitivity similar to that of $^{1}H$ and can therefore be used in MRS studies. It is the only naturally occurring fluorine isotope. Mobile $^{19}F$ is very scarce in the body and is biologically unimportant, so $^{19}F$ MRS has in general been performed on orally or parenterally administered biocompatible fluorocompounds. $^{19}F$ MRS has been successfully used to study blood substitutes (44), chemotherapeutic drugs (45), fluorinated anesthetics (46), metabolic markers (47), and enzymatic changes in animal brains with aging (48) and to determine concentrations of fluorinated neuroleptics, such as fluphenazine (49). Arndt et al. (50) carried out in vivo $^{19}F$ MRS of fluphenazine in the rat. They were able to spectroscopically localize the neuroleptic at the injection site and in vivo in the head. In vivo $^{19}F$ MRS has recently been used to detect trifluoperazine and fluoxetine in the brains of patients receiving these drugs (51). The ability to spectroscopically localize the biodistribution of fluorinated agents might help in monitoring the kinetics of psychotropic drug uptake from injection sites. With future developments in MRS technology it may be possible to measure concentrations of fluorinated neuroleptics and other psychotropic drugs in the human brain. By using fluorine-labeled substrates, such as 2-fluoro-2-deoxyglucose, it has been possible to follow glucose metabolism in rats (52). $^{19}$F MRS has also been used to measure cerebral blood flow (53).

### *$^{13}$C MRS*

Of the carbon that is "naturally abundant," i.e., occurs naturally in the human body, 98.9% is $^{12}$C, which is not detectable by MRS. The other 1.1% of naturally abundant carbon is $^{13}$C, the resonances of which are visible in extracts. MRS of rat brain using natural-abundance $^{13}$C demonstrates $^{13}$C chemical shifts of brain metabolites and provides important information about amino acid and neurotransmitter levels (glutamate, $\gamma$-aminobutyric acid) and some information about phospholipid metabolism and energy production (23).

Substrates labeled with $^{13}$C, such as glucose, have provided an elegant method to study selected areas of metabolism in vivo and in vitro. Behar et al. (54) localized [$^{13}$C]glucose signals in rabbit brain and were able to follow metabolism serially after intravenous [$^{13}$C]-glucose administration. The advantage of the $^{13}$C MRS studies is that metabolites of the parent compound are simultaneously detected, allowing flux through metabolic pathways to be analyzed in different physiological states and diseases.

### *$^{1}$H MRS*

In vivo application of $^{1}$H MRS has been slow. One limitation of $^{1}$H MRS is that the range of visible chemical shifts is much narrower (10 ppm) than that of $^{31}$P MRS (40 ppm). Thus, detection of individual resonances is more difficult. The advent of superconducting magnets with stronger fields will improve the resolution of $^{1}$H spectra.

MRS with $^{1}$H has revealed elevation of cerebral lactate levels during pharmacologically induced seizures in rabbits (55) and in a patient with focal epilepsy (56). $^{1}$H and $^{31}$P MRS in patients with hepatic encephalopathy (57) have revealed high levels of glutamine and phosphocholine and low levels of choline. By using $^{1}$H MRS, low levels of *N*-acetylaspartate (58) and high levels of lactate (59) have been found in patients with cerebrovascular disease. Significant abnormalities have also been observed in patients with multiple sclerosis (60). *N*-Acetylaspartate and phosphocreatinine resonances have been reported to be low in patients with meningiomas (61). Sharma et al. (62) recently obtained $^{1}$H spectra from the frontal and occipital regions of nine psychiatric patients and nine healthy comparison subjects. The patients, especially those who had bipolar disorders and had received lithium, had a higher ratio of *N*-acetylaspartate to phosphocreatinine than did the comparison subjects. Further studies are needed to explore this interesting observation.

### *$^{23}$Na MRS*

$^{23}$Na is 100% naturally abundant but has relatively low sensitivity, making it a poor choice for MRS. Another limitation of in vivo $^{23}$Na spectroscopy is that only 40% of the intracellular sodium is visible by MRS when the cell membranes are intact (63). Sodium exists in the form of the solvated cation and aqueous macromolecular complexes inside and outside the cell, and it exhibits very small chemical shifts (24). Use of agents that can selectively alter the extracellular $^{23}$Na chemical shift can allow the resolution of the extra- and intracellular pools into distinct resonances. The membrane-impermeable shift reagent dysprosium III phosphate, used for this purpose in animal and tissue studies, has not been used in humans because of toxicity.

The potential clinical applications of $^{23}$Na MRS include disorders involving sodium transport or membrane disruption. Studies using $^{23}$Na MRS without shift reagents show dramatically high levels of $^{23}$Na in patients with stroke, hemorrhage, and brain tumors (64).

### *$^{7}$Li MRS*

Lithium has established value in the prophylactic treatment of manic-depressive illness, the acute treatment of mania, and the treatment of some patients with schizophrenia. The molecular basis for the therapeutic effects of lithium is unknown at this time, although it has been postulated that lithium competes for the binding sites of such biological cations as $Na^+$, $K^+$, $Mg^{2+}$, and $Ca^{2+}$ and that lithium interacts with membrane phospholipids. Lithium inhibits the conversion of inositol phosphate to inositol and phosphate in the phosphatidylinositol second messenger pathway. In addition, a $^{7}$Li MRS study (65) has provided evidence that lithium interacts with the membrane-associated cytoskeleton in human erythrocytes. These observations taken together suggest that lithium interacts with important regulatory sites on the cytoplasmic surface of cellular membranes, and, therefore, $^{7}$Li MRS could be a valuable approach to studying the intracellular chemistry of lithium.

Recently, in vivo $^{7}$Li NMR studies were carried out with human subjects (66). In that study, the brain lithium levels measured by $^{7}$Li MRS correlated well with serum levels.

## POTENTIAL, PITFALLS, AND PROMISE

MRS has several unique advantages: it is noninvasive and therefore ideal for longitudinal studies; it provides information about intracellular pH, the motion of molecules, and their quantification that is not available by means of other techniques; and one can examine metabolic turnover directly and express it in moles per kilogram, the important units that describe chemical reactions.

There are limitations, however (6). MRS requires stronger and more homogeneous magnetic fields than MRI and also needs "shimming" for each measurement, making it more expensive in time and cost. Second, because the intrinsic sensitivity (ability to resonate) of some isotopes, such as $^{39}$K, is very low, they are inaccessible to MRS. Further, certain isotopes with high sensitivity, such as $^{19}$F, are present in the body in very low concentrations and therefore cannot be used in MRS studies in their natural state. The overall sensitivity of a given nucleus is its intrinsic sensitivity multiplied by its concentration in the tissue. In any given volume of interest, the current limit of detection is about $10^{-6}$ times that of water protons. Third, because the MRS signals are much weaker than the proton signals used for MRI, signal acquisition needs more time and the volume of interest has to be much larger than that for MRI. Fourth, only highly mobile nuclei that are in solution are visible to MRS. Nuclei whose mobility is restricted because of binding to membranes or macromolecules result in broad resonance signals with a poor signal-to-noise ratio. For this reason, only a few selected aspects of metabolism can be studied with MRS. Fifth, the information provided by MRS is purely chemical; approaches to spectral localization still involve problems. Sixth, the long acquisition time limits detection of transient biochemical changes. For this reason, MRS cannot yet be adequately applied in cognitive or neurophysiological challenge paradigms.

Several patient-related and technical variables need to be considered in interpreting MRS studies (67). The potential confounding effects of age and medication have already been discussed. Patient cooperation is a key factor as well. Motion artefacts (random patient motion, blood movement, or CSF motion) could affect the quality of spectra in MRS (68). Biochemical information provided by MRS usually conforms to geometrically shaped volumes (e.g., spherical) and not to the shapes of anatomical structures of interest to the psychiatrist; such partial volume effects must therefore be considered in all MRS studies (69). Finally, regional differences in brain structure (e.g., superficial versus deeper structures) could also affect the ability to interpret MRS data.

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) scans provide alternative, promising approaches to functional brain imaging. PET scanning has the advantages of relatively high sensitivity, high spatial resolution, and the ability to be used to investigate a wide range of biochemical processes, including glucose and oxygen consumption, neurotransmitter turnover, and neuroreceptor binding. The disadvantages include the use of radioactive tracers, with its attendant risks, and the need for an expensive cyclotron nearby to make such isotopes. SPECT scanning offers the advantages of not requiring such an expensive facility and the potential to provide information about a wide range of biochemical processes, but it has a relatively low resolution. Thus, it can be seen that PET and SPECT scanning have advantages not available with MRS; MRS likewise has unique advantages. These techniques may therefore be complementary and are likely to represent competitors among the developing brain imaging technologies.

To date, clinical application of MRS has mainly involved $^{31}$P. In view of their relatively high NMR sensitivities, the $^{1}$H metabolites, such as neurotransmitters and amino acids, are promising avenues for future research in clinical applications of MRS. Newer techniques involving suppression of signals from water and fat are likely to make this approach more feasible. $^{13}$C MRS and $^{23}$Na MRS are other noninvasive techniques for viewing brain chemistry. MRS with $^{7}$Li and $^{19}$F will offer new ways to study the kinetics and function of psychopharmacological agents. Future clinical applications also will benefit from the use of spectroscopy contrast agents that enhance chemical shift. Further improvements in the technology of localization will aid in obtaining metabolic images of special areas of interest in the brain. It is also conceivable that "metabolic maps" of the brain could be developed by simultaneous use of multinuclear spectroscopic techniques in vivo, e.g., using $^{31}$P nuclei for ATP and $^{1}$H for lactate. The technologies of MRI and MRS are likely to converge to yield spatial chemical images, which may result in novel approaches to clinical research.

The field of MRS is very young; it has been stated recently that nearly every study in MRS breaks new ground (5). Future studies of MRS in neuropsychiatry will need to address the following goals: 1) identifying and quantifying differences between carefully selected patients with major neuropsychiatric disorders and appropriate comparison subjects 2) re-examining in vivo information from patients in the light of modern neurochemistry, 3) examining relationships between structure and function by simultaneous use of MRI and MRS, and 4) studying biochemical variables to delineate treatment effects, establish predictors of treatment response, identify biological correlates of illness progression, and develop innovative treatment approaches.

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# Kleptomania: Making Sense of the Nonsensical

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*Objective: Kleptomania, or the irresistible impulse to steal unneeded objects, is a poorly understood disorder. The objectives of this paper are to critically review and integrate existing data and to make suggestions for further research. Data Collection: Information was gathered by reviewing the English-language literature on kleptomania. Cases were chosen for review that approximated the diagnosis as defined in* DSM-III-R. *These cases were analyzed in terms of their relationship to previous theories about the disorder, and larger relevant studies were examined. Using the data organized into a table, the author explores areas of convergence and disagreement and discusses the methodological difficulties of the different studies. Findings: Kleptomania is more common than previously thought. The "typical" individual with kleptomania is a 35-year-old woman who began to steal when she was 20 years old. Her thefts bring both relief and guilt. She probably has not sought treatment on her own but suffers from a necessary, pervasive, repetitive, and self-destructive act. She may have a history of sexual dysfunction or sexual preoccupation and may be unhappily married to an emotionally unsupportive husband. She has been labile and dysphoric for many years and may have a personality disorder. She has probably had a tumultuous, stressful childhood and may dissociate. Conclusions: The author proposes a biopsychosocial model of the etiology of kleptomania based on data from the literature. This model emphasizes possible childhood abuse as a precipitating factor in later development of kleptomania. More complete research is needed in the study of kleptomania.*

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> Yet I lusted to thieve and did it compelled by no hunger, nor poverty.
>
> —St. Augustine, *Confessions,* 370 A.D.

Kleptomania, or the irresistible impulse to steal unneeded objects, is a poorly understood disorder. Despite the strange and seemingly meaningless behavior that characterizes it, kleptomania has received little empirical attention. This is surprising in view of the fact that kleptomania may account for a substantial proportion of the staggering 40 billion dollars in business losses attributed to shoplifting each year (1). Additionally, people with kleptomania suffer the pain and humiliation of repeated arrests.

*DSM-III-R* classifies kleptomania as an impulse control disorder. The symptoms may begin in childhood and can continue intermittently throughout adulthood. *DSM-III-R* (pp. 322–323) describes the disorder as follows:

> The essential feature . . . is a recurrent failure to resist impulses to steal objects not needed for personal use or their monetary value; the objects taken are either given away, discarded, returned surreptitiously, or kept and hidden. Almost invariably the person has enough money to pay for the stolen objects. The person experiences an increasing sense of tension immediately before committing the act and intense gratification or relief while committing it. Although the theft does not occur when immediate arrest is probable . . . , it is not preplanned, and the chances of apprehension are not fully taken into account. The stealing is done without long-term planning and without assistance from, or collaboration with, others. Further, there is no association between the stealing and anger or vengeance.
>
> The diagnosis is not made if the stealing is due to Conduct Disorder or Antisocial Personality Disorder.

The term "kleptomania" (Greek for "stealing madness") did not appear until 1838 (2). However, court cases, personal accounts, and anecdotal reports throughout the ages have underscored the curious nature of

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this type of stealing (2–8) and have contributed to the current *DSM-III-R* nosology. In 1799, for example, a wealthy woman appeared before a British magistrate charged with the theft of a piece of lace (3). Some years later, according to Ray (4), Benjamin Rush remarked on the otherwise high moral character of afflicted individuals and further commented on the theft of a seemingly unneeded object. Esquirol, in describing the monomanias, discussed illnesses characterized by involuntary, irresistible actions (6). According to Gibbens and Prince (7), Esquirol and Marc coined the term "kleptomania" in 1838 to describe the behavior of several kings who stole worthless items.

Many modern writers have commented on kleptomania, and several psychoanalytic theories have been proposed to explain it. *DSM-I*, published in 1952, included "kleptomania" as a supplementary term because it was not yet considered a distinct diagnostic entity (2). The disorder was left out of *DSM-II* entirely. It found its way back into *DSM-III* and *DSM-III-R* as an impulse control disorder. (There is no substantial difference between the *DSM-III* and *DSM-III-R* definitions.)

This paper focuses on kleptomania or kleptomania-type disorders as opposed to stealing for profit, a distinction that has often been blurred in the literature. Perhaps because there seems to be no consistent theory regarding most aspects of the disorder and there is much theoretical overlap, many terms have been used to describe a variety of behaviors. For the sake of clarity, the terms "shoplifting" and "stealing" are used here to refer to a broad range of behaviors that include both kleptomania and theft for profit. "Kleptomania," however, is used to refer to a disorder approximating the *DSM-III-R* definition. Although the term "nonsensical stealing" does not necessarily match the *DSM-III-R* definition of kleptomania, it approximates the type of peculiar behavior seen in the disorder and will be used in this capacity.

The goals of this paper are 1) to provide a critical review of the literature on kleptomania, 2) to integrate existing data on kleptomania and kleptomania-type disorders and propose an etiological model, and 3) to offer suggestions for a more definitive, comprehensive study of the disorder.

## EPIDEMIOLOGY AND DEMOGRAPHICS

Kleptomania has been recognized for more than 150 years as a comparatively rare clinical condition. Table 1 summarizes the published English-language case studies approximating the *DSM-III-R* definition of kleptomania. Included in the table are categories that represent potential areas of disagreement and controversy as well as other important variables. Excluded from the table are cases that did not clearly conform to *DSM-III-R* criteria. The few larger studies of stealing (21–27) are discussed in the text. The difficult methodological problems inherent in a retrospective review of cases will be addressed in the discussion.

Table 1 shows that 22 of the 26 patients described in published reports did not seek voluntary treatment. They were either coerced into treatment by those who caught them or referred by the courts after apprehension. There is no information on this point about one case. Because most cases of kleptomania are identified through court-ordered evaluations of shoplifters, the rate of the disorder in the general population is unknown. There is disagreement regarding the rate among shoplifters. In one study of 338 arrested shoplifters (25), only 13 (3.8%) were considered to have displayed a "compulsive behavior pattern" that the authors called "kleptomania." Bradford and Balmaceda (26) found that two (4%) of 50 shoplifters met criteria for kleptomania approximating those of *DSM-III-R*, and Medlicott (14) found similarly diagnosed kleptomania in five (10%) of 50 people arrested for thefts of various kinds. Yates (21) found nonsensical stealing in 15 (15%) of 101 arrested shoplifters but did not specify whether these patients met the criteria for kleptomania. Another study (24) found "nonrational" stealing (stealing not motivated by conscious goal) in 32 (24%) of 132 arrested shoplifters. On the other hand, several authors of larger studies of people arrested or convicted of shoplifting (23, 27) failed to identify any subjects with kleptomania. This wide range of kleptomania rates probably reflects both the sampling and definitional difficulties inherent in the identification of the disorder.

Kleptomania may be more common than these statistics suggest. Indeed, studies of clinical samples not selected for kleptomania (28–31) found relatively high rates of the disorder. Hudson et al. (29), for example, found that 24% of a group of patients with bulimia met *DSM-III-R* criteria for kleptomania. Based on extrapolation of the rate of bulimia from prevalence studies of bulimia in a large nonreferred adolescent population (2.5%) (32), the rate of kleptomania is at least six per 1,000 persons. These data must be interpreted with great caution because the relationship between eating disorders and kleptomania is unclear. Furthermore, an estimate of the rate of kleptomania based on the comparison of two unrelated studies may not be reliable. Nonetheless, these data suggest that kleptomania occurs far more frequently than previously thought.

There are additional reasons for believing that kleptomania may be more extensive than earlier studies suggest. A high percentage of people steal, and most are never caught (16, 33, 34); those who witness a theft rarely report it. Arieff and Bowie (25) noted the possibility that no arrest is made when an accused shoplifter is a prominent social figure. Moreover, individuals with kleptomania tend to be ashamed of their behavior and hesitant to share their secret with anyone, including therapists. Thus, shoplifters in general and those with kleptomania specifically may escape detection. The disorder, even if rare, most certainly is a source of both tremendous economic loss for

**TABLE 1. Case Reports of *DSM-III-R* Kleptomania in the Literature**

| Author | Sex | Age (years) | Age at Onset (years) | Referral Source | Sexual Preoccupation/ Dysfunction/ Perversion | Relief or Pleasure[a] | Guilt[a] | History of Affective or Anxiety State | Symptoms Associated With a Personality Disorder |
|---|---|---|---|---|---|---|---|---|---|
| Fishbain (9) | F | 57 | 20 | Self | Yes | Both | —[b] | Depression | Histrionic |
| Turnbull (10) | F | 29 | 6 | —[c] | Yes | Both | Yes | —[b] | —[b] |
| | F | —[b] | —[b] | —[c] | Yes | —[b] | —[b] | Depression | Shy |
| | M | 25 | 14 | —[b] | Yes | —[b] | No | —[b] | —[b] |
| Keutzer (11) | F | 25 | —[d] | Self | Yes | —[b] | No | Psychotic depression, anxiety | —[b] |
| Elizur and Jaffe (12) | F | 25 | 6 | Self | Yes | Relief | Yes | —[b] | Compulsive, labile |
| Coid (13) | F | 54 | —[b] | Courts | Yes | Relief | Yes | Depression, anxiety | —[b] |
| Medlicott (14) | M | 52 | 14 | Courts | —[b] | Relief | —[b] | —[b] | —[b] |
| | M | 59 | —[b] | Courts | —[b] | Relief | —[b] | —[b] | Passive, unsuccessful |
| | M | 68 | 48 | Courts | —[b] | Relief | —[b] | —[b] | —[b] |
| | M | 47 | —[b] | Courts | —[b] | —[b] | —[b] | —[b] | —[b] |
| | F | 44 | 44 | Courts | —[b] | Both | Yes | —[b] | —[b] |
| Gauthier and Pellerin (15) | F | 30 | 26 | Courts | —[b] | —[b] | Yes | —[b] | —[b] |
| Russell (16) | F | 17 | 17 | Courts | —[b] | —[b] | —[b] | —[b] | —[b] |
| | F | 19 | 9 | Courts | Yes | Pleasure | —[b] | —[b] | Hysterical |
| McConaghy and Blaszczynski (17) | F | 39 | 23 | Courts | —[b] | —[b] | —[b] | Depression | —[b] |
| | F | 53 | 35 | Courts | —[b] | Relief | —[b] | —[b] | —[b] |
| Davis (18) | F | 42 | —[b] | Courts | —[b] | —[b] | —[b] | Depression, anxiety | Passive-dependent |
| | F | 48 | —[b] | Courts | —[b] | —[b] | —[b] | Depression, anxiety | —[b] |
| | F | 40 | —[b] | Courts | —[b] | —[b] | —[b] | Depression, anxiety | Lability |
| | F | 40 | —[b] | Courts | —[b] | —[b] | —[b] | Depression, anxiety | Lability |
| | F | 31 | —[b] | Courts | —[b] | —[b] | —[b] | Depression, anxiety | Lability, obsessive-compulsive, dependent |
| Gudjonsson (19) | F | —[e] | —[b] | Courts | Yes | Both | —[b] | Depression, anxiety | Obsessive-compulsive |
| McElroy et al. (20) | F | 23 | 20 | Courts | —[b] | Both | Yes | Bulimia | —[b] |
| | F | 35 | 20 | Courts | —[b] | Both | No | Bulimia, major depression | —[b] |
| | F | 19 | 16 | Courts | —[b] | —[b] | —[b] | Bulimia, major depression | —[b] |

[a] During or associated with the act of stealing.
[b] No information was available.
[c] Coerced into treatment after apprehension by peer or store owner.
[d] Childhood.
[e] Middle-aged when treated; thefts began 20 years earlier.

the community (1) and emotional trauma for those afflicted.

Another area of uncertainty concerns gender. Anecdotal case reports and some studies (18, 21) seem to agree with the longstanding belief that kleptomania occurs primarily in women. One study (27), however, contradicted that belief. In addition, Medlicott's study of 50 thieves (14) revealed that four of the five identified as having kleptomania were men. Of the 26 case studies listed in table 1, five were men and 21 were women. Similarly, Yates (21) found that 80% of people who engaged in nonsensical shoplifting were women.

The literature clearly suggests that the majority of those identified as having kleptomania are women. One reason may be that women are more likely than men to present for psychiatric evaluation (26). Indeed, table 1 shows that all three of the subjects who referred themselves were women. In addition, the courts may be likely to send male shoplifters to prison while sending female shoplifters for psychiatric evaluation. Medlicott (14), for example, reported the case of a male patient who was imprisoned for 14 years for the repetitive thefts of bicycles and trucks that he abandoned shortly after stealing. Thus, for several reasons, it is possible that men who shoplift do not enter the population of people referred for evaluation.

Another possibility is that kleptomania is truly more common among women. Guze (35) has shown that male and female felons from similar difficult environments may develop quite differently. Men may develop more overtly antisocial behavior, but women develop other symptoms, such as hysteria. Men and women with impulse control problems may manifest these

**TABLE 1 (continued)**

| Family History | Precipitant | Marital Status |
|---|---|---|
| Postpartum depression in mother | Yes | Married twice |
| Mother ineffectual, with somatic complaints; father absent | —[b] | Single |
| —[b] | Yes | Married |
| —[b] | Yes | Single |
| Depression in, suicide attempts by mother; father absent | —[b] | Single |
| Psychotic mother; weak father | —[b] | Married |
| Denied | Yes | Married twice |
| —[b] | —[b] | Single |
| —[b] | Yes | Married |
| —[b] | —[b] | Married |
| —[b] | —[b] | Married |
| —[b] | —[b] | Married |
| —[b] | —[b] | Married |
| —[b] | Yes | Single |
| —[b] | —[b] | Single |
| —[b] | Yes | Married |
| —[b] | Yes | Separated |
| —[b] | Yes | Married |
| —[b] | Yes | Married twice |
| —[b] | Yes | Married |
| —[b] | Yes | Single |
| —[b] | Yes | Married |
| Weak mother; cruel stepfather | Yes | Married |
| Major depression in mother | —[b] | Single |
| Major depression in grandmother; alcoholism in father; kleptomania, alcoholism, and bulimia in sister | —[b] | Married |
| Major depression in mother | —[b] | —[b] |

problems differently. Men seem to have a relative monopoly on the more aggressive acts of impulse such as pyromania, intermittent explosive disorder, and pathological gambling. Kleptomania and trichotillomania, the less overtly destructive impulse disorders, may be more common in women.

The mean±SD age at the time of evaluation for the women with kleptomania shown in table 1 was 35±12.6 years (range=17–57), for the men it was 50±16.1 (range =25–68), and for both sexes it was 38±14.3. The mean±SD age at onset for the women was 20±12.5 (range=6–44). (The data are insufficient to determine the mean age at onset for the men.) Although some individuals with kleptomania have been arrested numerous times, the typically long period of time between onset and presentation seems to reinforce the belief that kleptomania is a behavior that is extremely difficult to extinguish without help and that it is difficult to detect. The traditional notion of kleptomania first developing in a middle-aged woman in response to a loss, such as a child's leaving home, may be faulty. Instead, symptoms of kleptomania may return under these circumstances. It seems clear that the disorder is a pattern that is established early on.

Most of the individuals shown in table 1 were married (N=16) or separated (N=1). This supports Yates's data on marital status in 101 individuals with nonsensical shoplifting (21): 73% were married. There are few data on other demographic variables, such as social class, rural and urban distribution, race, and religion. Schlueter et al. (24), however, found that "nonrational" shoplifters were more likely to be of faiths other than Catholic or Protestant and tended to be well educated. They also found no significant difference in race between the "nonrational" thieves and ordinary thieves. Sampling difficulties undoubtedly affected the reliability of these data.

## ETIOLOGY, CHARACTERISTICS, AND CLASSIFICATION

### *Psychological and Psychosexual Theories*

Much of the literature regarding the causes of kleptomania focuses on its relationship to anxiety, depression, or sexual disturbances (10, 16, 21, 25, 36). According to Ellenberger (37), Janet felt that the need for stimulation resulted in artificial methods to increase psychological tension. In 1911, Janet discussed the case of a depressed woman who was able to relieve her symptoms through the stimulation provided by shoplifting. The need for stimulation is also echoed in Fishbain's case of a depressed woman who masturbated during shoplifting (9). Fishbain concluded that depression was a stimulus to risk-taking behavior (kleptomania), which had an antidepressant effect. Roy (36) felt that the new onset of shoplifting in an otherwise normal man was a symptom of stress, but others (13, 38) have considered the function of kleptomania to be symptom relief. Although this theory does not explain why these patients choose theft as a relief mechanism, this model seems, at least in part, valid. Indeed, all 13 of the individuals for whom such information was reported in table 1 experienced relief of tension or both relief and pleasure from stealing.

Depressive states and tension are often reported as precursors to many kinds of theft (18, 21, 26). Yates (21) found depression in 80% of those who engaged in nonsensical shoplifting. Indeed, table 1 reveals that 13 of the 14 individuals for whom a history of affective or anxiety states were reported had states of depression or depression and anxiety. Unfortunately, in the majority of cases reported, neither the severity of the depressive or anxiety state nor the length of the episode was specified. In most cases, however, no mention was made of hospitalization; most cases seem to have involved outpatient evaluation and treatment. There is descriptive evidence, however, that the individuals suffered from a spectrum of affective states ranging from dysthymia to psychotic depression. This range of mood raises the question of the length of time the person has experienced anxiety or depression—i.e., whether an acute, chronic, or recurring mood disorder is more likely to be associated with kleptomania. This information is not found in most case descriptions. Further evidence supportive of an association between kleptomania and depression, however, comes from studies of subjects with bulimia (28–31). McElroy et al. (20), noting that both the impulse to steal and bulimic behavior ceased with antidepressant therapy, highlighted the possible link between kleptomania and depression. Although some have felt that depression might have been a response to an approaching trial, Davis (18) noted that depression predated arrest.

The same ambiguity in the literature holds true for acute environmental precipitants to stealing, which may or may not be sequentially related to the onset of affective or anxiety states. All 14 of the individuals in table 1 for whom the data were available reported precipitants to their stealing behavior. Cupchik and Atcheson (1), in discussing thievery among "upstanding" citizens (some of whom may have had kleptomania), formulated the loss-substitution-by-shoplifting hypothesis based on the recollections of individuals who had recently been arrested. These authors maintained that in a large percentage of patients the theft was an effort to obtain symbolic compensation for an actual or anticipated loss. The study, like most others, was retrospective and uncontrolled.

With a few exceptions, the literature is vague in its description of precipitants and stressors and in its methodology. Many cases were retrospective and not the result of longitudinal exploration. Vague terms like "social isolation" (21) were used in descriptions. However, since there was a disparity between age at onset and age at evaluation, the information about the precipitant to the latest theft seems of limited value. The chronicity of the depression and/or tension and the importance of acute precipitants in disorders that are chronic are unclear. The chances seem good that individuals with kleptomania have experienced one precipitant after another for many years and have existed in a chronic depressed or anxious state for many years. Indeed, Yates (21) suggested that nonsensical shoplifting may be associated with an accumulation of stressors over time. Few, if any, authors who noted objective precipitants in their subjects explored the intrapsychic mechanisms that were stimulated by these precipitants. Since the materials stolen were not for their economic value, one plausible hypothesis is that the theft was for intrapsychic profit. As shown later in this paper, analytic theorists have advocated this idea. Most of the case descriptions in the literature, however, fail to identify the patient's thoughts or associations just before the theft.

Fenichel (39) believed that kleptomania can have direct sexual significance. Other early drive theorists felt that kleptomania involved "doing a forbidden thing secretly" and likened the behavior to a sexual act. Wittels (40, 41), for example, observed that stealing was the sex life of the person with kleptomania and that his or her real sex life was underdeveloped. According to Elizur and Jaffe (12), Stekel felt that kleptomania was analogous to a perversion. The stolen objects have also been considered to have other sexual significance. Fenichel (39) suggested that the objects stolen by individuals with "perverse" kleptomania are actually their fetishes. Wise (42) commented that kleptomania and other impulse disorders have been associated with fetishistic behavior. Bradford and Balmaceda (26), however, failed to find evidence of "sexual deviation" in their two subjects with kleptomania.

No information was given concerning sexual preoccupations, behaviors, or dysfunction for 17 of the 26 patients in table 1. In the nine studies reporting such information, the patients reported experiences such as vaginismus, nonarousal, promiscuity alternating with abstinence, and a preoccupation with sterility. Some reported orgasm or sexual excitement during thefts (9–13, 16, 19). In the light of the absence of information on the majority of patients, it is unwise to make firm conclusions. Certainly, there are also biases built into this information. Indeed, an author treating several patients with kleptomania, one of whom has a strange sexual behavior, is more likely to report this case rather than the others. The data, however, suggest an association between kleptomania and sexual abnormalities. Several authors (4, 43–46) have argued that kleptomania is more prevalent during menstruation or pregnancy, but these observations have not been duplicated (12, 27) and are not considered valid.

The psychoanalytic literature suggests that kleptomania is a symptom of an underlying conflict. Noting the presence of depression and disturbed sexuality, analysts proposed mechanisms they felt could explain the disorder. Fenichel (39) and others (41, 43, 47–50) discussed kleptomania and other forms of stealing as the gratification of id impulses and as an expression of infantile needs. Abraham (51) traced kleptomania back to the child's feelings of neglect concerning proofs of love: in stealing, the child finds a substitute pleasure for a lost pleasure and simultaneously takes revenge on those who caused the suffering. Unfortunately, there are no modern data available to refute or confirm these earlier psychoanalytic findings. Indeed, most modern case reports of kleptomania are essentially devoid of important details such as associations and transference phenomena. Family data are also scarce. Such information would theoretically reflect the nature of the individual's psychosexual development and could be used to refute or confirm analytic theory. Of the 26 case studies summarized in table 1, family characteristics were dealt with in only nine. In one case, the subject's mother was psychotic, in four cases the mother was depressed, and in two cases the mother was ineffectual or absent. Absent or weak fathers were reported in three of the nine cases. One case described a cruel stepfather and one described an alcoholic father. These data are undoubtedly incomplete, and little can be said conclusively about family characteristics, but these findings may lend support to the idea that kleptomania is related to depression.

Some authors (12, 39, 52) focused not only on the act but on the specific, symbolic meaning of the objects stolen and their relationship to fixation points. An oral fixation would mean that the stolen object represents mother's milk, anal fixation is linked to the hoarding and collecting of goods, and phallic fixation results in penis envy or castration fears—the stolen object represents a penis. Wittels (40) theorized that individuals with kleptomania take "love in the shape adequate to their libidinal understanding." Perhaps, therefore, they can be either oedipal or pre-oedipal; it is quite difficult to arrive at a determination of the primitiveness of the defenses of individuals with kleptomania from available data. However, personality traits (discussed later in this paper) may provide some additional information. There is not enough information to know whether a given person both hoards and discards or what the significance of keeping the stolen objects would be. It would be interesting to know whether one person stole only one type of article, but this cannot be gleaned from the available data.

With a slow shift away from traditional drive theory, some writers have chosen to see kleptomania itself as defensive (49, 53–55). Rado (53), in discussing castration anxiety in women, considered the "fight" defense as the primary source of pleasure in kleptomania. According to this view, the woman, overcome by castration fear, acquires a penis to strengthen her "tottering phallic position." Menaker (49), in a study of 12 boys who stole, felt that the only defense against the strong passive-receptive wish is the opposite wish to grab, steal, or tear away. In general, these authors were moving away from the notion of theft as having a primarily sexual meaning to a model of theft as defensive.

Although these analytic writers discussed theft and not kleptomania specifically, they seemed to consider the two to have the same meanings and causes. Yates (21), however, has shown that there are many important differences between stealing for obvious profit and nonsensical stealing. For example, she said, those who steal for profit tend to have, among other things, far more "anti-social and delinquency-prone personalities," whereas individuals with kleptomania tend to be depressed and socially isolated. There appears to be a difference in character that goes unexplained by early analytic cases. One wonders why the thief and the kleptomaniac are discussed interchangeably when they may, in fact, develop so differently. Guze (35), however, pointed out that male and female felons growing up in similar tumultuous environments may develop different symptoms as adults. It remains unclear, however, whether it is accurate to draw conclusions about the individual with kleptomania from the psychoanalysis of other kinds of thieves.

In this light, other writers view kleptomania as a form of psychopathy or related to it (12, 40, 41, 46, 54). Wittels (40) believed that individuals with kleptomania enter treatment only when threatened by the law and abruptly abandon treatment once they have been acquitted. Elizur and Jaffe (12) saw kleptomania as a neurotic conflict in a person with elements of an antisocial character formation. The notion of guilt and remorse has prompted several writers to comment on the role of the superego in stealing, the presence or absence of guilt, and the presence or absence of symbolism in stealing acts. Some (56, 57) have felt that theft results from a hypertrophied superego, which ultimately results in incarceration or other punishment. Moore's "episodic" shoplifters (22) stole items used for self-punishment. Castelnuovo-Tedesco (58), in describing an ordinary thief as a kleptomaniac, maintained that stealing is done with superego approval based on primitive ethical premises, but other authors (12, 41, 49) felt that the superego is underdeveloped in kleptomania.

Those theories which view the individual with kleptomania as having an antisocial character seem particularly narrow. Indeed, the drive to steal in kleptomania may be no more antisocial than the need to lie to the physician about the quantity of food intake in anorexia nervosa. Moore's shoplifters (22) responded with "quiet compliance" when detected. Furthermore, they felt that their acts were illegal and morally wrong. The data in table 1 also seem to contradict the idea that kleptomania is simply antisocial. Of the nine subjects for whom such information was reported, six expressed guilt regarding the act of theft. (Yates's finding of a lack of antisocial traits in her patients [21] seems to support these findings.) Of course, these observations are based on limited data, and it is possible that the expression of guilt could have been a ploy to escape further legal action. There is no information, however, on those who are not apprehended, and it is possible that patients who have been caught reflect a different subgroup of individuals with kleptomania. Perhaps these patients have a more hypertrophied or punitive superego and "set themselves up" to get caught more easily than those whose superegos are underdeveloped. Testing this hypothesis would present difficult methodological problems.

The issue of personality is briefly mentioned in *DSM-III-R*, as is the idea that kleptomania sometimes, but not invariably, is associated with personality disorders. In some ways, the question of personality may be rooted in the question of whether kleptomania exists as a monomania or as one of the pathological signs in an otherwise normal person. The literature seems to suggest that there can often be associated personality symptoms. Table 1 reveals that many of the reported cases had such symptoms. Ten of the reports described characteristics consistent with personality disorders. These included compulsiveness, dependency, lability, hysteria, and histrionics—most considered to be more primitive traits. Unfortunately, as with many other categories, nothing is known about the 16 cases that did not report personality characteristics, making generalizations difficult. In addition, the lack of a reliable longitudinal evaluation in many of the cases makes a diagnosis of personality disorder tenuous. However, many of the symptoms seem more consistent with a character disorder than symptoms of, for example, a depressive episode. Additionally, individuals with kleptomania and nonsensical shoplifting reported tumultuous and unusually stressful childhoods (concentration camp survival, for example), marital turmoil, social isolation, and lack of self-esteem (11, 12, 16, 18, 19, 21, 22), making associated personality difficulties all the more possible.

Like earlier analytic writers, many object relations theorists did not seem to distinguish between kleptomania and stealing for profit. Object relations models emphasize internal representations of the infant's relationships with its objects as well as the importance of id desires and affective states (59). Castelnuovo-Tedesco (58), for example, felt that stealing and kleptomania represent "a way of controlling a frightening and dangerous object and rendering it harmless by reinstating a long-lost but greatly cherished sense of omnipotence." There does seem to be an attitude of omnipotence in some patients (18), but this does not always appear to be conscious. Indeed, the fact that the individual may steal in plain view of others may reflect this attitude. Winnicott (60), although not discussing kleptomania specifically, felt that the child who steals is looking for the mother over whom he or she has rights. The mother becomes the object that the child is ready to find.

Self theory is concerned with deficits in the structure of the self as opposed to the conflict resolution associated with drive theory (59). Kligerman (61), for example, in response to Castelnuovo-Tedesco (58), discussed stealing and kleptomania in terms of the narcissistic vulnerabilities found in disorders of the self. He postulated that stealing can be a response to narcissistic injuries and can help prevent fragmentation of the self. Both of these authors also questioned whether all stealing, including ordinary theft, is symbolic and psychopathological. Castelnuovo-Tedesco concluded that the act of stealing has many meanings and functions, all of which are restitutive. Tolpin (62) saw his patient's kleptomania as an attempt to counter an inadequate formation of her nuclear self. However, his patient's clinical picture was complicated by her ongoing substance abuse.

Several authors (63–65), perhaps noting its repetitive, irresistible, and seemingly meaningless patterns, have likened kleptomania to or considered it a part of an obsessive-compulsive disorder. Laughlin (64), however, pointed out the differences between the two disorders, including the propensity to act out in kleptomania. The behavior in obsessive-compulsive disorder is not an end in itself but is instead intended to produce or prevent some future event or situation. Furthermore, *DSM-III-R* points out that the act of kleptomania may bring intense gratification—an experience that helps differentiate the impulse disorders from obsessive-compulsive disorder. This seems to be an important distinction because obsessive-compulsive disorder is noteworthy for its ego dystonicity and its sense of relief rather than gratification. An examination of table 1, however, reveals that in the 13 cases reporting symptoms of relief and/or gratification from the stealing act, six reported relief, six reported both pleasure and relief, and one reported only pleasure. Thus, stealing does not appear to be strictly pleasurable and many subjects with kleptomania seem to obtain relief from the act, implying that a relationship might exist between kleptomania and obsessive-compulsive disorder.

In summary, analysts and other dynamic psychotherapists have suggested many mechanisms to explain both the developmental origins and behavior of the person with kleptomania. There appears to be some agreement regarding the types of symptoms seen in the disorder but little agreement about causation. Most theories do not seem specific for kleptomania and can be used to describe a multitude of disorders. Furthermore, there has been little integration of the various schools of thought. It must be noted that most seem to ignore the intensity of the symptoms and fail to explain the tremendous, uncontrollable drive to repeat what most certainly is self-destructive, masochistic behavior—behavior that overpowers, controls, and imprisons. Not all theorists feel that acts of self-destruction are adequately explained by traditional analytic tenets. Simpson and Porter (66), for example, felt that "self-destructive activities were not primarily related to conflict, guilt, and superego pressure, but to more primitive behavior patterns originating in painful encounters with hostile caretakers during the first years of life."

### *Biological Considerations*

A number of reports suggested that kleptomania-type behavior can be organically precipitated by neurological conditions (67–71), medication effects (72), and other medical conditions (73). Mendez (67) described a 71-year-old man with dementia and left frontal and right parietotemporal hypolucency who started stealing objects when he was 66 years old. Khan and Martin (68) reported the case of a 25-year-old man with presenile cortical atrophy (particularly frontal) who stole cigarette stubs and broken saucers as well as objects of greater value. Chiswick (69) described a middle-aged woman who, 2 years before a nonsensical stealing episode, had a right parietal mass accompanied by apathy and depression. She could not recall her stealing episode and had continued blackouts. She was effectively treated with amitriptyline, phenytoin, and psychotherapy. Chiswick considered psychomotor attacks as the cause of the stealing but felt that depression was the likely precipitant. Bleuler (45) discussed a disturbance in consciousness in his patients with kleptomania, as did Bradford and Balmaceda (26), who found that 12% of a group of shoplifters described a dissociative state. According to Elizur and Jaffe (12), Stekel felt that kleptomania necessitated a fugue state. Zoric et al. (70) described nonsensical shoplifting in a woman who suffered from narcolepsy. Moak et al. (71) speculated that lower levels of biogenic amines and rates of synthesis in the elderly lead to a decline in reciprocal inhibition and may cause stealing. Todd (72) described a woman on "calmative" medication with no previous criminal record who stole food from a store for no apparent reason. Segal (73) described unwitting shoplifting by a person with severe hypoglycemia secondary to an insulinoma.

The data available must be interpreted with caution—it is, for example, difficult to know whether the given localizations of lesions were specifically responsible for the stealing. Obvious pathology in one part of the brain can affect other distant areas. Additionally, data that describe parietotemporal lesions may be suggestive of temporal lobe epilepsy. Indeed, many of the symptoms described can be attributed to temporal lobe epilepsy—altered sexuality, dissociative phenomena, depression, and anxiety. However, like most hypotheses regarding kleptomania, there are not yet enough clinical data to support or refute these ideas.

There are not enough data to know whether these organically ill patients have had the same developmental and psychological characteristics and circumstances that seem to be more frequent in those with the "naturally occurring" form of kleptomania. Although the cases lack obvious signs of relief or gratification, they may nonetheless be reflective of a biological substrate that bypasses the developmentally driven features of a person suffering from kleptomania.

### *Behavioral Models*

Unfortunately, data regarding behavioral models are scarce because many behavioral researchers are not concerned with etiology. Indeed, all of the reports found in the literature focused almost exclusively on treatment. Glover (74), however, suggested that her patient's positive response to a trial of covert sensitization implicitly supports a cognitively mediated model of compulsive shoplifting. The development of an etiological model based on response to treatment, however, must be made with caution.

## TREATMENT AND PROGNOSIS

Because most available data on kleptomania focus on describing the phenomenon, very few reports of successful treatment exist and long-term follow-up is lacking. Aversive behavioral treatment, which pairs an aversive consequence of stealing with the desire to steal, has been used. Keutzer (11) had her patient hold her breath when she thought of stealing to rid her of the desire to steal; this treatment was successful at 10-week follow-up. A more lengthy follow-up period may have been helpful in determining the efficacy of this form of treatment.

Covert sensitization pairs an imagined consequence of stealing with the desire to steal. To treat a woman who had stolen daily for 14 years, Glover (74) had the patient associate images of nausea and vomiting with the desire to steal. At 19-month follow-up this patient had had only one episode of stealing. Gauthier and Pellerin (15) also reported successful use of this technique at long-term follow-up.

Although much of the theoretical groundwork has been provided by the psychoanalytic community, there is little well-organized information regarding the efficacy of long-term insight-oriented psychotherapy. Psychoanalysts and other psychodynamic therapists have claimed success by treating kleptomania and other forms of stealing as a symptom of an underlying conflict (47, 48). It is not at all clear whether treatment successes are specific for kleptomania, especially because the definitions of the disorder in these reports are so murky and variable.

Fishbain (9) used several forms of treatment to cure his patient of kleptomania. He used insight-oriented and supportive therapies for the patient's "risk-taking" behavior and her guilt feelings related to the effect of her kleptomania on her family, respectively. He also prescribed medication for depression and behavioral modification for the actual stealing. He noted that depression and stealing returned on discontinuation of antidepressant medication. These results seem to indicate that an appropriate treatment for kleptomania is antidepressant therapy, but other authors (17, 19) reported no cessation of kleptomania with antidepressants. McElroy et al. (20) found that administration of serotonergic agents resulted in complete or partial cessation of stealing in three patients with both bulimia and kleptomania. McElroy et al. concluded that because appetite, impulsivity, and mood can be affected by serotonergic pathways, these drugs may be helpful in the treatment of these conditions.

Although many methods have been used to treat kleptomania, perhaps the most common is the self-imposed banning of all shopping in an attempt to prevent theft. Although there have been several reports of this self-treatment (17, 19, 20, 74), it may be far more common than reported because individuals with kleptomania can impose such "treatment" on themselves without having to seek professional help.

## DISCUSSION

### *Methodological Difficulties*

The compiling of data for table 1 was complicated by a lack of complete information. This incompleteness may be a reflection of the individual authors' attempts to illustrate one or two points about a particular case. Many of the anecdotal reports are based on short-term interviews rather than longitudinal encounters. Secret characteristics, early trauma, and repressed precipitants, therefore, may not be reflected. This lack of data undoubtedly affects reliability. Additionally, the phenomenon of underreporting important details may be a reflection of the covert actions and secret nature of the individual with kleptomania rather than the deficiency of the reporting authors. Also, most of the cases in table 1 were referred from courts. These are characteristics of patients who were caught; the table tells us nothing about those who elude apprehension. Furthermore, many of these cases were undoubtedly chosen for review and publication on the basis of characteristics such as sexual dysfunction. It is not known whether the authors cited excluded cases without these interesting features.

On the other hand, the analysis of these cases is meant to give an overview of available data. Despite the various limitations that bias each reported case, it is hoped that the information gleaned can be of assistance in determining more about this mysterious illness and can prompt further thought.

### *Integration of Existing Data*

Although there is no unified psychological theory regarding kleptomania's etiology, the small amount of information available affords us a basis on which we can hypothesize about the disorder. It would appear that the average person suffering from kleptomania is a 35-year-old married woman who has been apprehended for the theft of objects she could easily afford and does not need. Her stealing began at age 20 and she has been caught several times. A search of her house reveals piles of unopened packages of stockings and cans of jam. Her acts of theft bring her great relief from tension, and she may attempt to force herself to remain indoors for fear that she will steal. Despite her sense of entitlement about the thefts, she feels remorse and almost never seeks treatment on her own. Perhaps because of guilt or shame or because she is fearful of losing the opportunity to steal, she feels compelled to kept it a secret. She seems to suffer from a powerfully necessary, pervasive, repetitive, and ultimately self-destructive act. A personal history reveals that she is unhappily married, may have sexual difficulties, and has been dysphoric and moody for many years. She very likely has had a tumultuous and stressful childhood. Furthermore, she may have a personality disorder.

In general, theorists have seemed to focus on the unusual symptoms of kleptomania rather than examining the overall clinical picture. In examining the data available to us, many of the details presented here seem to raise the possibility of the role of early sexual or physical trauma. Indeed, many of the characteristics found in those who have been sexually abused (75, 76) seem to correspond well with the traits of those who have kleptomania. Several statistics illustrate this point. In a study of sexually abused women, Herman (76) discovered that, like women with kleptomania, many women who had been sexually abused as children complained of major depressive symptoms in adult life and suffered from alternating sexual promiscuity and abstinence. Like those with kleptomania (10, 11, 15, 17–19), sexually abused women developed stormy and tormented relationships, often with exploitative men. They often felt unvalued by their husbands, and many had relationships with older men. More than half complained of sexual impairment—a phenomenon found with some regularity in individuals with kleptomania. Indeed, there are many examples of sexual preoccupations and intrusive sexual fantasies in kleptomania that correspond to those of sexually abused women. Herman (76) stated that some sexually abused women "so thoroughly associated sex with the feeling of being dominated and controlled that they were unable to relax." Similarly, Turnbull (10) reported the case of a woman with kleptomania who was passive during sex and had fantasies of being beaten by an older woman, which led to orgasm. Dissociative phenomena, which have been described in those with kleptomania, are also seen with regularity in those suffering from early abuse (75).

Another relevant phenomenon, which perhaps has stood in the way of our more fully understanding the illness, is the secretiveness of the behavior in kleptomania. Indeed, by its very nature, kleptomania is covert and secretive—much like its sufferers. Could this be a reflection of the secrets (either conscious or unconscious) that those who have been abused keep?

If the literature is accurate, individuals with kleptomania appear to suffer from many abuses—in childhood, marriage, and relationships. This may give us some clues as to the origins of the compulsive, addictive symptoms. Van der Kolk (77), for example, felt that trauma can be repeated on many different levels, including behavioral, emotional, physiological, and neuroendocrine, and that it is associated with physiological hyperarousal and the compulsion to repeat the trauma.

According to both animal and human studies (77), those who have been exposed to severe stress will experience large increases in endogenous opiates and catecholamines in response to subsequent stress. This chemical shift can produce relief, dependence, and withdrawal resembling the response to exogenous opioids. The victims neutralize their hyperarousal, which interferes with their ability to make rational decisions, by a variety of addictive behaviors, including compulsive reexposure to situations reminiscent of the trauma, such as abusive relationships. Applied to kleptomania, Van der Kolk's theory could posit that the stimulus of theft may condition an opioid response. Kleptomania may be the mechanism by which the person attempts to modulate affective states, gain relief from hyperarousal, and prevent withdrawal from the addiction (kleptomania).

Individuals who have been traumatized may show an initially good social adjustment but become socially isolated or aggressive when emotionally aroused. They also can respond inappropriately to sexual arousal (77). This might help to explain the bizarre sexual behavior and ideation of some individuals with kleptomania as well as their isolation and aggression (theft).

Although the reminiscence of original trauma in kleptomania may be in a tumultuous marriage, perhaps the theft itself can serve as a representation of the trauma—such as "stealing" the father from the mother during the father's exploitation of oedipal longings or the compulsion to repeat receiving inappropriate and dangerous "gifts" from the father. It may also represent an identification with the aggressor—the woman with kleptomania may become like the person who robbed her of her childhood. Thus, it is possible that kleptomania is a self-abusive behavior that is used in the service of modulating affective states and as a coping mechanism. Perhaps the act itself is a repetitive trauma. Each theft elicits a necessary physiological response, the positive reward of which becomes learned and repeated and is representative of a dynamic reenactment. In the sexually abused, these adaptive behaviors ultimately perpetuate chronic feelings of helplessness, a sense of being bad, and a sense of loss of control (77). These feelings and behaviors can lead to great social and personal suffering (77)—traits that those with kleptomania are well acquainted with.

## CONCLUSIONS

A more complete biological, behavioral, and developmental understanding of kleptomania would help alleviate both tremendous cost to the public and untold human suffering. Future research seems to be dependent on the collection of a larger group of individuals with the illness. Certainly, prospective studies would be desirable. Due to the covert nature of the illness and the hesitation of those afflicted to come forward, obtaining a large group presents the clinician with a challenging task. Prevalence studies using an inventory designed to detect other impulse disorders (78) have been successful and may be an important first step in studying the illness.

If study groups are selected from the courts, more complete, longitudinal evaluations should be performed. Once a population can be identified, sexual abuse inventories should be used (79), results of medication trials should be recorded, and evidence of dissociation and other necessary information should be gathered (80). Controlled studies comparing subjects with kleptomania with other thieves as well as with a variety of nonforensic populations and subjects with other types of impulse control disorders should be conducted.

Therapists need to improve their ability to detect all of the secretive impulse disorders—a task that requires patience. Indeed, the detection of kleptomania, like the detection of other sensitive issues, may necessitate a lengthy, alliance-based psychotherapy. The initial answer to a therapist's questions about a history of secretive, impulsive, or compulsive behavior is often negative. It is not until later in the therapeutic process, when a firm therapeutic alliance has been established, that the patient feels free to disclose such behavior. A nonjudgmental inquiry during an initial evaluation may allow the patient to bring it up at a later date.

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# Patient Predictors of Response to Psychotherapy and Pharmacotherapy: Findings in the NIMH Treatment of Depression Collaborative Research Program

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*Objective: The authors investigated patient characteristics predictive of treatment response in the National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program. Method: Two hundred thirty-nine outpatients with major depressive disorder according to the Research Diagnostic Criteria entered a 16-week multicenter clinical trial and were randomly assigned to interpersonal psychotherapy, cognitive-behavior therapy, imipramine with clinical management, or placebo with clinical management. Pretreatment sociodemographic features, diagnosis, course of illness, function, personality, and symptoms were studied to identify patient predictors of depression severity (measured with the Hamilton Rating Scale for Depression) and complete response (measured with the Hamilton scale and the Beck Depression Inventory). Results: One hundred sixty-two patients completed the entire 16-week trial. Six patient characteristics, in addition to depression severity previously reported, predicted outcome across all treatments: social dysfunction, cognitive dysfunction, expectation of improvement, endogenous depression, double depression, and duration of current episode. Significant patient predictors of differential treatment outcome were identified. 1) Low social dysfunction predicted superior response to interpersonal psychotherapy. 2) Low cognitive dysfunction predicted superior response to cognitive-behavior therapy and to imipramine. 3) High work dysfunction predicted superior response to imipramine. 4) High depression severity and impairment of function predicted superior response to imipramine and to interpersonal psychotherapy. Conclusions: The results demonstrate the relevance of patient characteristics, including social, cognitive, and work function, for prediction of the outcome of major depressive disorder. They provide indirect evidence of treatment specificity by identifying characteristics responsive to different modalities, which may be of value in the selection of patients for alternative treatments.*

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In the effort to understand the variability of response to treatments for depression, the relevance of patient characteristics has received much attention. Nevertheless, relatively little systematic research has examined the predictive value of these characteristics in studies comparing different forms of psychotherapy and pharmacotherapy. Certain characteristics of the patient and the nature of the depression may be general indicators of prognosis irrespective of treatment, while others may be indicators of response to individual treatments alone or of differential treatment outcome, that is, preferential response to one or more treatments compared to others. The elucidation of predictors of response addresses an important aspect of treatment specificity by characterizing the type of patients for whom a treatment is most or least effective; it could also have direct clinical applicability in the selection of patients for the most appropriate treatment modality. In addition, some predictors of response to treatment may provide indirect evidence about the putative specific mechanism of a particular modality by indicating patient characteristics that are especially responsive to it, such as functional and relational capacities or type of depression. This may be especially important because only limited evidence about differential treatment effects on measures of outcome hypothesized to be specific to each modality has emerged from this study (1, 2). Although we chose to consider patient characteristics initially, since there is some indication from the literature (3, 4) that they have greater influence on outcome, we plan to address therapist, relationship, and process variables in future analyses.

Comprehensive reviews of general predictors of response to psychotherapy (5, 6) and to tricyclic antidepressants (7–9) reveal that the literature is characterized by lack of consensus about or replication of many findings. The general predictors of response to psychotherapy that have emerged have been derived from many studies based on various psychotherapies, often in small and heterogeneous samples of patients with diverse disorders. Other major reasons for the inconsistent findings among studies include lack of specification of the treatment, variability of inclusion and diagnostic criteria, lack of standardization of outcome measures, variability of criteria for improvement, and differences in selection of patient variables and measures investigated.

The purpose of this article is to report the patient characteristics that predicted treatment response in the National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program (10), which was the first multicenter, comparative clinical treatment trial in the field of psychotherapy research initiated by NIMH. This study compared the efficacy of interpersonal psychotherapy, cognitive-behavior therapy, imipramine with clinical management (as a standard reference condition), and placebo with clinical management (as a control condition) for outpatients with nonbipolar, nonpsychotic major depressive disorder.

Several features of the Collaborative Research Program clinical trial design were considered advantageous for the study of the relation of patient predictors to treatment outcome. First, the multisite, common protocol design permitted study of a larger sample than do most single-site studies, but with uniformity of diagnosis and severity of depression across sites. Second, the extraordinary standardization of the therapies—with treatment manuals, therapist training, and monitoring of the quality of performance—would enhance the prediction of response to specific treatments by reducing the variability of the treatments themselves. Third, the use of a control condition, placebo with clinical management, would help differentiate predictors of response to specific treatments from predictors of general response or response to nonspecific treatment. Fourth, the use of standard outcome measures and response criteria would permit better comparison with the results of other studies. We examined predictors in two groups of patients: 1) those who completed the course of treatment, in order to search for predictors of outcome when there was full exposure to the specific ingredients of the therapies, and 2) all of those who entered the treatment trial, including those who withdrew before completion, in order to search for predictors of the full range of outcomes.

In previous single-site comparative treatment studies of interpersonal psychotherapy and cognitive-behavior therapy whose results would be most comparable to those of the NIMH Treatment of Depression Collaborative Research Program, some patient predictors of response to psychotherapy and tricyclic antidepressants were reported. Among the six studies that reported patient predictors of response to cognitive-behavior therapy, one (11) found that pretreatment symptom severity was significantly associated with negative outcome at termination, while another (12) reported an association with positive outcome. Inconsistent findings were reported for endogenous depression (13, 14). Learned resourcefulness, assessed by the Self-Control Schedule, was found to be related to positive outcome (11, 15). Cognitive dysfunction, as measured by the Dysfunctional Attitude Scale, predicted poor response at termination for group cognitive-behavior therapy (16) and negative outcome at 1-year follow-up, though not at termination, for individual cognitive-behavior therapy (17).

Among studies of patient predictors of outcome in interpersonal psychotherapy, initial social adjustment on the Social Adjustment Scale and an index of emotional freedom, education, and occupation predicted positive outcome in social adjustment but not depression severity (4). Endogenous depression was associated with poorer outcome for interpersonal psychotherapy than for tricyclic or combination treatment (18). Situational depression was associated with favorable response to either interpersonal psychotherapy or a tricyclic antidepressant (19).

Among these studies, there were several patient characteristics that predicted response to tricyclic antidepressants. Endogenous depression was associated with favorable outcome with an antidepressant alone or in combination with interpersonal psychotherapy (18), as well as good outcome for patients who completed treatment, but poor outcome for those who dropped out (14). Depression severity was related to negative outcome (11), and learned resourcefulness was related to poor response (15).

## METHOD

A common protocol was conducted at three clinical research sites with a prospective, random-assignment, placebo-controlled design, double-blind for pharmacotherapy and with independent, blind clinical evaluation. A detailed description of the background and design of the main treatment study and the pilot training study has been previously published (10).

The subjects were male and female outpatients between the ages of 21 and 60 years who met the Research Diagnostic Criteria (RDC) for a current, definite episode of major depressive disorder on the basis of the Schedule for Affective Disorders and Schizophrenia (SADS) (20) structured interview and who had a score of 14 or more on the 17-item modified version of the Hamilton Rating Scale for Depression (21) for at least 2 weeks before initial screening and again at rescreening after a 1- to 2-week wait or drug washout period. Exclusion criteria consisted of other specific psychiatric disorders, medical contraindications for the use of imipramine, concurrent psychiatric treatment, current active suicide potential, and need for immediate treatment. Patients were clinically referred, voluntary research subjects who gave written informed consent to participate.

All 28 therapists were experienced psychiatrists and psychologists who had received further clinical training by independent expert trainers and had met competence criteria in order to participate. Their performance was monitored throughout the study (10, 22–24). Treatments were conducted in accord with detailed manuals that specified the theoretical rationale, strategies, techniques, and boundaries of each modality (25–27). All treatments were planned to be 16 weeks in duration and to consist of 16–20 sessions. The pharmacotherapy dosage schedule was flexible, with a goal of 200 mg and a maximum of 300 mg. The clinical management component for the pharmacotherapy conditions provided not only guidelines for medication monitoring and management but also support, encouragement, and advice as necessary, although specific psychotherapy interventions were proscribed.

The total sample (N=239) comprised all patients who actually entered treatment from among the 250 patients who met inclusion criteria and were randomly assigned. The completer sample comprised only the patients who completed at least 12 sessions and 15 weeks of treatment and had clinical evaluations at termination. Clinical evaluations were available for 155 patients on the Hamilton depression scale for analyses of depression severity and for 156 patients for analyses of complete response (because of the inclusion of an additional patient for whom the Beck inventory score only was available). There were no statistically significant differences between treatments in overall attrition, treatment-related attrition, or symptomatic failure. Seven patients did not have termination evaluations (1). The findings on comparative treatment efficacy with regard to depressive symptoms and general functioning, modality-specific measures of change, and the temporal course of treatment effect have been reported elsewhere (1, 2, and manuscript by J.T. Watkins et al., submitted for publication).

A comprehensive review of the literature was undertaken to identify patient predictors of response to cognitive-behavior therapy, interpersonal psychotherapy, and psychotherapy in general, as well as to tricyclic antidepressants and imipramine in particular. Among the predictor variables for which there was evidence of stability and replication, a limited set of independent variables for the multivariate analyses was selected on the basis of the distribution, intercorrelation, reliability, and face validity of the relevant measures. Personality disorders were added on the basis of experience in the pilot study. Because of the potential importance of a cognitive function predictor for cognitive-behavior therapy, the Dysfunctional Attitude Scale total score was selected on an exploratory basis. Two subsequent reports suggesting its relationship to outcome (see the beginning of this article) confirmed that decision.

The 26 independent variables were grouped within three domains: 1) sociodemographic variables—age, sex, marital status, social class; 2) diagnostic and course variables—endogenous, recurrent, primary, situational, and double depression, melancholia, family history of affective disorder, age at onset of first episode, duration of current episode, acuteness of onset of current episode, and number of previous episodes; and 3) function, personality, and symptom variables—social dysfunction, work dysfunction, cognitive dysfunction, social satisfaction, expectation of improvement, number of personality disorders, dramatic personality disorder, odd personality disorder, anxiety, somatization/hypochondriasis, and interpersonal sensitivity.

The dependent measures of depression outcome at termination were 1) complete response, a stringent categorical measure based on the combination of a 17-item Hamilton depression scale score less than or equal to 6 and a Beck Depression Inventory (28) score less than or equal to 9, and 2) depression severity, a continuous measure based on the 23-item Hamilton depression scale score, which included cognitive and atypical vegetative symptom items. Two dependent variables were selected to examine predictors of complete response or remission and change in the severity of depression, which would reflect partial response as well. One measure was based solely on clinical evaluator ratings, while the other also incorporated patient self-reports. Scores were based on ratings at termination of treatment for completers and on the last rating obtained for patients who were withdrawn or dropped out (generally, at either interim or early termination evaluation, but for 20 early dropouts, at rescreening evaluation). The interrater reliability, as assessed by intraclass correlation coefficients, for the Hamilton 17-item scale score ranged from 0.92 to 0.96 across sites and from 0.90 to 0.98 within sites; for the Hamilton 23-item scale score it ranged from 0.93 to 0.96 across sites and from 0.89 to 0.98 within sites. The Beck inventory total score showed good internal consistency, with an alpha coefficient equal to 0.78. The percentages of patients achieving complete response were 43.6% (N=68) and 31.4% (N=75) in the completer and total samples, respectively. The mean±SD depression severity scores at termination were 9.43±7.33 and 13.92±10.19 in the completer and total samples, respectively.

### Data Analysis

To reduce further the number of independent patient variables from the initial set of 26 for the main predictor analyses across treatments, preliminary multiple regression analyses were conducted within each individual treatment condition, and only the most consistent predictors of outcome within individual treatments were selected for the main analyses. In both the total sample and the completer sample, initial analyses were conducted for independent variables in each of the three single domains, and then the "best" subsets of predictor variables within each domain were combined, with the pretreatment Hamilton depression score included, in final analyses conducted for each outcome measure. For these preliminary analyses we used the method of all possible subsets regression (29), which examines all possible models containing the independent variables and selects the "best" subsets on the basis of an algorithm that uses the criterion of minimal Mallow's $C_p$ (30) to select the regression model which minimizes the total mean squared error and bias. Each variable in the model contributed a minimum of 2% of the variance to the adjusted $R^2$ value and had a regression coefficient significant at $p<0.10$.

The subsets of predictor variables that emerged from these multiple regression analyses together constitute a model which best predicts outcome and are indicators of the relative likelihood of favorable or unfavorable outcome for each individual treatment. It should be emphasized, however, that the results do not identify the relative importance of any single variable, since the effect of each variable on outcome variance takes into account the partial effects of all of the other variables in the model. We recognize that, given the number of initial patient variables and the size of the groups in the individual treatment conditions, there is an increased risk of chance findings because of the inherent limitations of the regression analytic approach. We therefore consider these analyses exploratory in nature. While certain predictor relationships replicated earlier findings, other predictors will require further attempts to replicate.

The main data analyses examined the evidence for possible predictors of outcome across all treatments and of differential outcome among treatments. Only 13 variables were selected for these analyses, which were the most consistent predictors of outcome in the final regression analyses within individual treatments, having been predictors in at least two of the four analyses and at a level of significance of $p<0.05$ in at least one. For depression severity as a continuous measure of outcome, analyses of covariance (ANCOVAs) were performed, with treatment (four levels) and predictors (two or more levels) as factors in the design and with pretreatment depression severity and marital status as covariates. Marital status was included because it was significantly related to outcome and unevenly distributed among treatment conditions. For continuous predictor variables, patients were divided into two groups by using a median split in score. Significant main effects identified patient variables that predicted outcome across treatments. Significant Predictor by Treatment interactions identified differential treatment effects of patient variables on outcome. For complete response as a categorical measure of outcome, log linear analyses (Treatment by Predictor by Response) were performed, and the "best fit" models were examined for predictor main effects as well as Predictor by Treatment interactions. A significance level of $p<0.10$ was chosen for the overall difference among treatments. The Bonferroni correction for multiple comparisons was used, so for any individual treatment comparison the obtained probability level had to be $<0.017$ to be considered significant at an adjusted alpha level of $<0.10$.

## RESULTS

### Preliminary Predictors Within Individual Treatments

*Cognitive-behavior therapy.* The most consistent predictor findings indicated that patients were relatively more responsive to cognitive-behavior therapy if there was lower initial cognitive dysfunction, briefer duration of the current episode of depression, absence of a family history of affective disorder, later age at onset, and a history of more previous episodes of depression. Furthermore, among completers, married patients were relatively more responsive to this therapy.

*Interpersonal psychotherapy.* Less social dysfunction was associated with complete response in both samples, accounting for 12%–13% of the outcome variance, and was also associated with good outcome on depression severity in the total sample. The most consistent predictor findings demonstrated that pa-

**TABLE 1. Patient Variables Studied for Their Effect on Outcome of a Trial of Psychotherapy or Pharmacotherapy in a Sample of Depressed Patients**

| Variable | Instrument | Patients Who Completed Therapy Trial (N=162)[a,b] | Total Group of Patients (N=239)[b] |
|---|---|---|---|
| Age (years) | Sociodemographic form | | |
| Mean | | 35.3 | 35.0 |
| SD | | 8.2 | 8.5 |
| Sex (female) | Sociodemographic form | | |
| N | | 109 | 168 |
| % | | 67.3 | 70.3 |
| Marital status | Sociodemographic form | | |
| Married | | | |
| N | | 67 | 96 |
| % | | 41.4 | 40.2 |
| Single | | | |
| N | | 37 | 63 |
| % | | 22.8 | 26.4 |
| Separated/divorced/widowed | | | |
| N | | 58 | 80 |
| % | | 35.8 | 33.5 |
| Endogenous depression | Research Diagnostic Criteria | | |
| N | | 64 | 91 |
| % | | 39.5 | 38.1 |
| Double depression[c] | Research Diagnostic Criteria | | |
| N | | 43 | 71 |
| % | | 26.7 | 29.8 |
| Family history of affective disorder | Family psychiatric history[d] | | |
| N | | 40 | 68 |
| % | | 24.8 | 28.6 |
| Duration of current episode >6 months | Research Diagnostic Criteria | | |
| N | | 97 | 141 |
| % | | 59.9 | 59.0 |
| Acuteness of onset (<3 months) | Schedule for Affective Disorders and Schizophrenia | | |
| N | | 68 | 100 |
| % | | 42.2 | 42.0 |
| Cognitive dysfunction score | Dysfunctional Attitude Scale[e] | | |
| Mean | | 141.6 | 139.3 |
| SD | | 35.6 | 34.9 |
| Social dysfunction score | Social Adjustment Scale[f] | | |
| Mean | | 2.9 | 2.9 |
| SD | | 0.8 | 0.7 |
| Work dysfunction score | Social Adjustment Scale[g] | | |
| Mean | | 2.7 | 2.7 |
| SD | | 0.8 | 0.8 |
| Anxiety score | Schedule for Affective Disorders and Schizophrenia[h] | | |
| Mean | | 12.0 | 12.4 |
| SD | | 4.6 | 4.7 |
| Patient expectation of improvement (much or completely better) | Attitudes and expectations form[i] | | |
| N | | 115 | 162 |
| % | | 71.0 | 68.1 |

[a] Includes seven patients who completed the trial but did not have termination evaluations.
[b] Percents are based on slightly varying Ns because of missing data in some instances.
[c] Defined as major depressive disorder plus chronic minor depression or intermittent depressive disorder.
[d] Presence of family history indicated by confirmed diagnosis of depression or mania in the patient's parents, siblings, or children.
[e] Total scale score, where a low score indicates the absence of dysfunctional attitudes (range=0–280).
[f] Mean for 11 items in social and leisure activities subscale, where a low score indicates the absence of impairment (range=1–5).
[g] Mean for applicable items in the work outside the house, work at home, and student subscales, where a low score indicates the absence of impairment (range=1–5).
[h] Sum of five subscale items including panic and psychic and somatic anxiety symptoms (range=4–30).
[i] Patient's global response regarding his or her expectation of improvement with treatment.

tients, particularly males, who had a lower pretreatment level of social dysfunction, who were separated or divorced, and who had higher interpersonal sensitivity and overall higher satisfaction with social relationships were more responsive to interpersonal psychotherapy. In addition, there was some evidence that patients with more acute onset and endogenous depressive episodes but not double depression responded more favorably to this psychotherapy.

*Imipramine with clinical management (imipramine-*

**TABLE 2. Patient Predictor Main Effects for Two Measures of Outcome in Depressed Patients Who Completed a Trial of Psychotherapy or Pharmacotherapy**

| | Outcome Measure | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Depression Severity (N=155) | | | | | | Complete Response (N=156) | | | | | |
| | Patients With Scores Below Median or Depression Subtype Absent | | Patients With Scores Above Median or Depression Subtype Present | | ANCOVA | | Patients With Scores Below Median or Depression Subtype Absent | | Patients With Scores Above Median or Depression Subtype Present | | Log Linear Analysis | |
| Predictor Variable | Adjusted Mean | SE | Adjusted Mean | SE | F (df=1, 144) | p | N | % | N | % | $\chi^2$ (df=1) | p |
| Cognitive dysfunction | 8.5 | 0.8 | 10.7 | 0.8 | 3.6 | 0.06 | 43/79 | 54 | 25/77 | 32 | 8.0 | 0.005 |
| Patient expectation of improvement | 11.4 | 1.1 | 8.8 | 0.7 | 4.3 | 0.04 | 53/111 | 48 | 15/45 | 33 | 2.6 | 0.11 |
| Endogenous depression | 10.5 | 0.8 | 8.1 | 0.9 | 3.9 | 0.02 | 37/94 | 39 | 31/62 | 50 | 2.0 | n.s. |
| Double depression | 8.6 | 0.7 | 11.5 | 1.1 | 4.9[a] | 0.04 | 52/115 | 45 | 16/40 | 40 | 0.2 | n.s. |
| Social dysfunction | 9.8 | 0.9 | 9.6 | 0.8 | 0.0 | n.s. | 39/76 | 51 | 29/80 | 36 | 2.8 | 0.09 |
| Age | 8.7 | 0.9 | 10.3 | 0.8 | 1.7 | n.s. | 40/76 | 53 | 28/80 | 35 | 4.5 | 0.03 |

[a] df=1, 143.

CM). Higher work dysfunction was the most robust predictor of good outcome with imipramine-CM in the completer sample for both complete response and depression severity. The most consistent predictor findings indicated that, overall, the patients who showed the most work dysfunction responded best to the effects of imipramine-CM, as did those with highest depression severity and endogenous or primary depression, but those with dramatic personality disorder responded poorly. In the total sample, patients who were not married, had a high level of cognitive dysfunction, or had a low expectation of improvement with treatment responded more poorly.

*Placebo with clinical management (placebo-CM).* Among the more consistent predictors, patients of younger age and with higher expectation of improvement appeared to respond more favorably to placebo-CM. Patients with higher levels of initial anxiety and depression severity responded less favorably, as did patients with double depression, who had a lower likelihood of complete response. Low cognitive dysfunction and dramatic personality disorder were associated with worse outcome on depression severity in the total sample only, suggesting a possible relation to attrition in this condition.

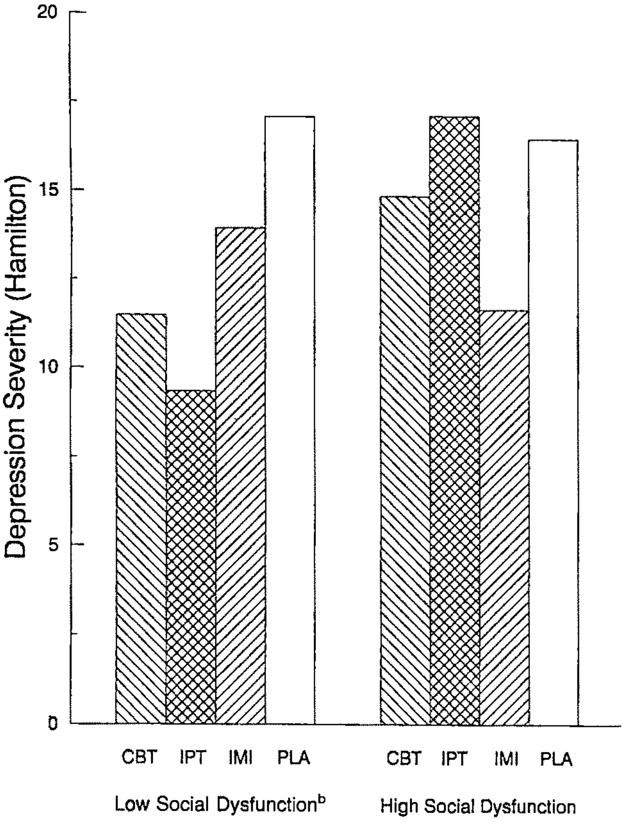
### *Main Predictors of Response Across Treatments*

The 13 variables most consistently predictive of outcome within treatments, which were selected for examination of potential prediction of outcome across all treatments or of differential outcome among treatments, were age, sex, marital status, endogenous depression, double depression, family history of affective disorder, duration of current episode, acuteness of onset, cognitive dysfunction, social dysfunction, work dysfunction, anxiety, and patient expectation of improvement. Table 1 shows their distribution in both samples, the instruments with which they were assessed, and notes on their content and scoring.

*Overall predictor effects.* Six patient predictors of outcome of the episode of depression across all treatment conditions were identified from the main effects in the ANCOVAs and log linear analyses in the completer sample (table 2), and another predictor was identified in the total sample only. Lower cognitive dysfunction and higher patient expectation of improvement were significantly associated with both a greater likelihood of complete response and a lower level of depression severity at termination. Significant main effects for expectation of improvement were also present in the total sample for both measures, and a trend effect was present for cognitive dysfunction on complete response. Although not evident in the completer sample, shorter duration of the current episode was significantly associated with both complete response ($\chi^2$=2.9, df=1, p=0.09) and lower depression severity (F=5.43, df=1, 228, p=0.02) in the total sample, suggesting that the influence of length of episode on recovery was more notable among patients who discontinued treatment, particularly in the placebo condition.

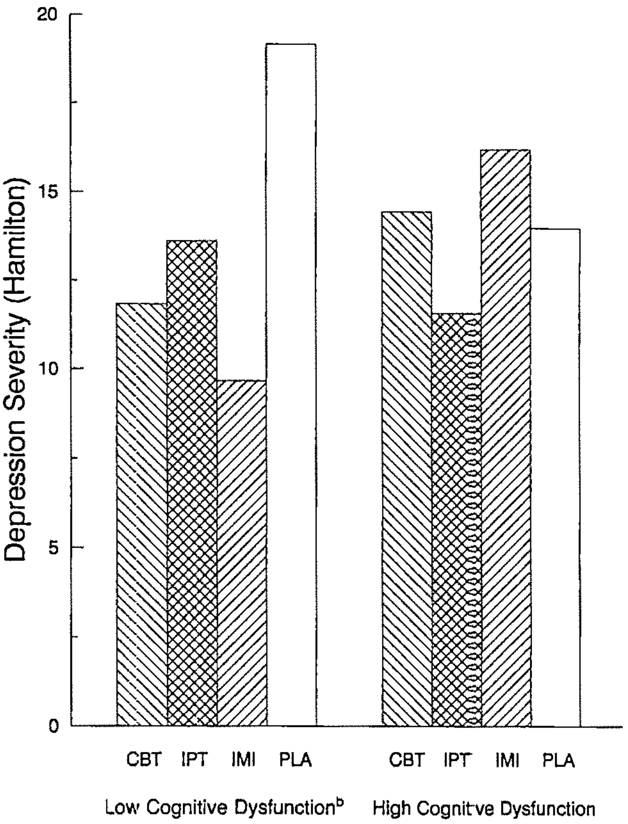
Endogenous depression was significantly associated with lower depression severity, whereas double depression was associated with higher depression severity, in both the completer and total samples. However, neither variable predicted complete response, suggesting a relation to residual depressive symptoms but not remission per se across all conditions. Lower social dysfunction was significantly associated with a greater likelihood of complete response in both samples but was not related to level of residual depressive symptoms. There was one significant main effect of age on complete response in the completer sample only, with older patients less responsive, particularly in the pharmacotherapy conditions.

FIGURE 1. Social Dysfunction as a Predictor of Differential Response to Treatment in the Total Sample of Depressed Patients (N=239)[a]



[a] CBT=cognitive-behavior therapy; IPT=interpersonal psychotherapy; IMI=imipramine; PLA=placebo.
[b] IPT significantly less than PLA (t=3.6, df=65, p=0.0005).

FIGURE 2. Cognitive Dysfunction as a Predictor of Differential Response to Treatment in the Total Sample of Depressed Patients (N=239)[a]

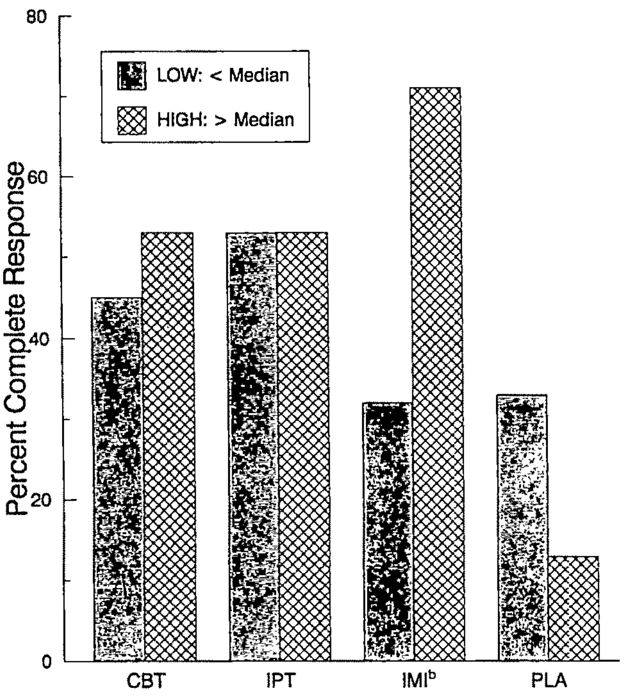


[a] CBT=cognitive-behavior therapy; IPT=interpersonal psychotherapy; IMI=imipramine; PLA=placebo.
[b] IMI significantly less than PLA (t=3.8, df=59, p=0.0003); CBT significantly less than PLA (t=2.7, df=56, p=0.009).

*Differential predictor effects.* In the ANCOVAs, two of the variables, social dysfunction and cognitive dysfunction, demonstrated significant differential treatment effects on depression severity as outcome in the total sample. Because of considerable heterogeneity of regression with regard to pretreatment depression severity, these analyses included only marital status as a covariate. For social dysfunction (figure 1), as measured by the score on the social and leisure activities subscale of the Social Adjustment Scale, there was a significant overall Treatment by Predictor interaction (F=2.84, df=3, 229, p=0.04). When the sample was divided at the median score into high and low social dysfunction, the significant treatment effect appeared only in the group with low social dysfunction (F=4.37, df=3, 116, p=0.006), such that interpersonal psychotherapy patients had the lowest mean depression severity scores at termination, significantly superior to scores in the placebo-CM group. Although there were no significant differences among treatments in the group with high social dysfunction (F=1.44, df=3, 111, n.s.), it should be noted that interpersonal psychotherapy patients had the highest mean severity in that group and the lowest severity in the low social dysfunction group. Thus, level of social functioning most differentiated treatment response among patients who received interpersonal psychotherapy.

For cognitive dysfunction (figure 2), as measured by the total score on the Dysfunctional Attitude Scale, there was a significant overall Treatment by Predictor interaction (F=4.27, df=3, 229, p=0.005) in the total sample. When separate ANCOVAs were performed for the high and low cognitive dysfunction groups divided at the median, the significant treatment effect appeared only in the low cognitive dysfunction group (F=4.97, df=3, 112, p=0.003), such that patients who received imipramine-CM and patients who received cognitive-behavior therapy had significantly lower depression severity scores at termination than patients who received placebo-CM. Treatment with imipramine-CM yielded the lowest mean depression severity score. Among the high cognitive dysfunction group, there were no significant differences between any of the active treatments and placebo-CM treatment (F=1.56, df=3, 115, n.s.). It is important to note that neither predictor directly distinguished differential

**FIGURE 3. Work Dysfunction as a Predictor of Differential Response to Treatment in the Completer Sample of Depressed Patients (N= 150)**[a]



[a]CBT=cognitive-behavior therapy; IPT=interpersonal psychotherapy; IMI=imipramine; PLA=placebo. "Median" refers to score on work dysfunction.
[b]Low significantly less than high ($\chi^2$=3.7, df=1, p=0.06).

response among the three active treatments, but only between the active treatments and the placebo-CM condition. For the patients who completed treatment, there were no significant Treatment by Predictor interactions at the $p<0.10$ level in the ANCOVAs, although the order of treatment effects was the same.

Log linear analyses also demonstrated significant Treatment by Predictor by Outcome interactions, indicating prediction of differential treatment effects for complete response (Hamilton depression score less than or equal to 6 and Beck inventory score less than or equal to 9) by three predictor variables: social dysfunction, cognitive dysfunction, and work dysfunction. For social dysfunction there was a significant interaction ($\chi^2$=7.0, df=3, p=0.07), and the significant treatment effect was for interpersonal psychotherapy, indicating that patients with low social dysfunction in the total sample treated with interpersonal psychotherapy had a significantly greater chance of complete response than those with high social dysfunction (odds ratio=5.2; $\chi^2$=7.4, df=1, $p<0.01$). For cognitive dysfunction there was also a significant interaction ($\chi^2$= 6.9, df=3, p=0.08), and the significant treatment effect was for imipramine-CM, demonstrating that patients with low cognitive dysfunction in the total sample had a significantly greater chance of complete response if they were treated with imipramine-CM than did those with high cognitive dysfunction (odds ratio=4.6; $\chi^2$=5.8, df=1, $p<0.05$).

There was a further significant interaction for work dysfunction ($\chi^2$=6.7, df=3, p=0.08) (figure 3), and the significant treatment effect was again for imipramine-CM, indicating that patients with high work dysfunction in the completer sample who were treated with imipramine-CM had a significantly greater chance of complete response than those with low work dysfunction (odds ratio=5.0; $\chi^2$=3.7, df=1, p=0.06).

## DISCUSSION

The results of this collaborative clinical treatment trial comparing the efficacy of two specific forms of psychotherapy with active and placebo pharmacotherapy demonstrate the relevance of patient characteristics for the prediction of outcome from an episode of major depressive disorder. Several characteristics of the depressive episode and patient functioning and cognition were indicators of overall prognosis without regard to the specific treatment received. These six patient predictors of depression severity or complete response were social dysfunction, cognitive dysfunction, patient expectation of improvement, endogenous depression, double depression, and duration of current episode.

The results of these analyses also provide evidence for a limited number of characteristics of patient function that significantly predicted differential response to psychotherapy or pharmacotherapy with imipramine compared to placebo. There were no significant predictors of differential response among the three active treatments. Among patients with better initial social adjustment (e.g., low social dysfunction), those who received interpersonal psychotherapy became significantly less depressed than those who received placebo-CM and had a higher rate of complete response than those with high social dysfunction. Among patients with less perfectionistic and socially dependent attitudes (e.g., low cognitive dysfunction), those who received treatment with imipramine-CM or cognitive-behavior therapy became significantly less depressed than those who received placebo-CM, and those treated with imipramine-CM also had a higher rate of complete response than those with high cognitive dysfunction. Among patients with more impairment of function at work, school, or home (e.g., high work dysfunction), those who received imipramine-CM had a higher rate of complete response than those with low work dysfunction. The differential predictor effects of social and cognitive dysfunction were observed in the total sample only, which may have been because of 1) the larger size of the total sample, 2) the comparison with all placebo-treated patients rather than placebo completers only, or 3) the inclusion of the full range of outcomes, including attrition, thereby reflecting differential acceptability of the treatments, an important aspect of effectiveness. These differential patient predictors may also provide indirect evidence of the specificity of the treatments by identifying characteristics most responsive to those modalities.

We consider the findings that emerged from both the main analyses across treatments and the preliminary multiple regression analyses within individual treatment conditions exploratory in nature and in need of further replication. The main data analyses (ANCOVAs and log linear analyses) were based on 13 independent variables and 52 analyses (two dependent variables and two samples); with an alpha level of 0.10, approximately one predictor and five analyses would be expected to be significant by chance alone. Although eight variables were identified as significant predictors and there were 16 significant main effects and five interactions among the analyses, some findings (i.e., for age) may have been chance effects and may not be replicable. With the number of initial patient variables and the size of the samples within the preliminary individual treatment analyses, there is a greater risk of chance findings, considering the inherent limitations of the multiple regression analytic approach. Nevertheless, where the interesting patterns of predictors of response within individual treatment conditions are consistent with the results of the main analyses, we include them, with appropriate statistical caution, in the discussion. Given the historical difficulty of replicating predictors across studies, we have emphasized in our interpretation the consistent pattern of findings across samples and measures of outcome. We believe that the main results may be of both theoretical and clinical interest, particularly because of the uncommon effort to compare predictors of differential outcome with a placebo control.

Our finding that social dysfunction was a significant predictor of differential response to interpersonal psychotherapy is consistent with the finding from the individual treatment analyses that greater impairment in social function was associated with poorer response to interpersonal psychotherapy on measures of severity and recovery from depression. One previous study of interpersonal psychotherapy (4) reported that good initial social adjustment predicted good outcome at termination for depressed patients, but only on measures of social function, not depression. Another psychotherapy study (31) also reported that pretreatment social function predicted social function at termination. The finding that favorable response to interpersonal psychotherapy is associated not only with good social adjustment but with previous attainment of a marital relationship, higher satisfaction with social relationships in general, and heightened interpersonal sensitivity seems consistent with reports in the general psychotherapy literature that various indicators of social competence or achievement are associated with good psychotherapy response, whereas social impairment is not. Poor social skills and poor interpersonal relationships have been reported to be related to poor outcome of psychotherapy (32, 33), while perceived social support, social satisfaction, and the ability to develop a good relationship have been associated with favorable response to psychotherapy (31, 34–38). However, this specific relation with pretreatment social adjustment was neither observed nor previously reported for patients treated with cognitive-behavior therapy, the other psychotherapy in our study. Thus, while the study shows that low social dysfunction predicts favorable general prognosis for outcome from depression, it also provides evidence of a specific responsiveness to interpersonal psychotherapy among those patients.

Less impairment in cognitive function as measured by the Dysfunctional Attitude Scale appears to be a general predictor of good prognosis as well as a specific predictor of good response to cognitive-behavior therapy (on depression severity) and imipramine-CM (on both outcome measures). In the two previous studies that examined the relation of dysfunctional attitudes to treatment response, high cognitive dysfunction was also associated with poor outcome at the termination of group cognitive-behavior therapy (16) and poor outcome at 1-year follow-up after individual cognitive-behavior therapy (17). Although in our study cognitive-behavior therapy appeared specifically to improve dysfunctional attitudes concerning the need for social approval (2), there was a less favorable antidepressant response to cognitive-behavior therapy in patients with greater cognitive dysfunction. This pattern of findings suggests that there may be an important distinction between the empirical effects of cognitive techniques in changing dysfunctional attitudes and a theory that links the presence of dysfunctional attitudes in depression to a preferential response to cognitive therapy.

To our knowledge, the relation of dysfunctional attitudes to outcome with other psychotherapies or pharmacotherapy has not been reported. The finding that in the total sample, low cognitive dysfunction predicted greater likelihood of complete response and greater improvement in depression severity for patients treated with imipramine-CM than for patients treated with placebo-CM was unanticipated. The better outcome of patients who expressed less socially dependent and perfectionistic attitudes may be consistent with the early reports that patients with neurotic (particularly, histrionic and labile) traits and with personality disorders respond poorly to tricyclic antidepressants (7, 39–42). Conversely, the differential predictor and individual treatment results suggest that patients with more socially dependent, dysfunctional attitudes may be more responsive to placebo treatment (3). The possible relation of these attitudes to drug therapy compliance, tolerance of side effects, and acceptance of pharmacotherapy remains to be understood.

Cognitive dysfunction did not predict poor response to interpersonal psychotherapy in this study. Indeed, it appears that the least cognitively impaired patients responded more favorably to cognitive therapy, and the least socially impaired patients responded most favorably to interpersonal psychotherapy. One possible explanation for these results is that each psychotherapy relies on specific and different learning techniques to alleviate depression, and thus each may depend on an adequate capacity in the corresponding sphere of patient function to produce recovery with the use of that approach. Therefore, patients with good social function may be better able to take advantage of interpersonal strategies to recover from depression, while patients without severe dysfunctional attitudes may better utilize cognitive techniques to restore mood and behavior. Patients with more impairment in social or cognitive function might be further overwhelmed and demoralized by a treatment approach that requires reliance on those capacities to achieve improvement. Such patients might respond better to an alternative psychotherapy or combination treatment or require longer-term psychotherapeutic intervention.

Work dysfunction is a major aspect of overall social adjustment in depression, measuring impaired performance, subjective distress, and interpersonal function. Among patients who completed treatment with imipramine-CM, impairment of work function was a significant differential predictor of recovery, and the results on both outcome measures within the individual treatment analyses were consistent. On the contrary, in the few previous studies, social impairment, work disability, and poor employment history have been related to poor outcome with antidepressant medication (39, 43). However, in our study imipramine-CM was previously reported (1) to show consistent, significant superiority over placebo-CM on measures of recovery and symptomatic improvement among the more severely impaired and depressed patients, as defined by the Global Assessment Scale. Furthermore, we observed (manuscript by J.T. Watkins et al., submitted for publication) that imipramine-CM had a significant early advantage for improvement in global social adjustment at 4 weeks and 12 weeks of treatment among the more severely depressed patients. To the extent that impaired work function in depression may result from diminished interest, energy, initiative, and concentration, psychomotor retardation, and social withdrawal, preferential improvement with imipramine would be consistent with the recognized clinical effects of tricyclic antidepressants on these symptoms. This pattern of findings suggests that more severe depression, impairment, and work dysfunction are patient characteristics which are especially responsive to pharmacotherapy with imipramine and which may be of value in the selection of patients for this modality.

In this study endogenous depression was an overall predictor of lower depression severity at termination across all conditions. Previous studies, though, have reported that endogenous depression is a negative indicator of response to psychotherapy, both interpersonal psychotherapy (18) and cognitive-behavior therapy (13). However, Kovacs et al. (14) found endogenous depression to be a positive predictor of outcome for patients who completed treatment with either a tricyclic antidepressant or cognitive-behavior therapy, while Blackburn et al. (44) found no effect of endogenous features on response to either treatment. In our individual treatment analyses for interpersonal psychotherapy, endogenous depression predicted reduction of depression severity. This relationship was not observed for cognitive-behavior therapy. In the individual treatment analyses for imipramine-CM, our finding that endogenous depression was associated with complete response and depression severity corroborates the many previous reports that the endogenous subtype of depression is a major indicator of response to tricyclic antidepressants (7, 14, 18, 19, 45). The lack of differential predictive effect for endogenous depression may be a result of measuring outcome after 4 months, since the differential effect of imipramine-CM on endogenous symptoms was most manifest at 8 and 12 weeks of treatment (manuscript by J.T. Watkins et al., submitted for publication). The reports of situational depression as a predictor of negative outcome for tricyclics and positive outcome for psychotherapy were not replicated, however.

The presence of double depression and the duration of the depressive episode are important aspects of the course of illness that appear to influence response to treatment. In a large naturalistic study uncontrolled for treatment, double depression was associated with favorable outcome from the major depressive episode only, but with poor outcome if outcome was defined as full recovery from the underlying chronic minor depression as well (46–48). In our controlled treatment trial, double depression was predictive of higher depression severity at termination but not of complete response, suggesting a relation to degree of improvement but not remission per se across all treatment conditions. Within the individual treatment analyses, double depression predicted lack of complete response from the episode among patients treated with placebo-CM but not among those who received one of the three active treatments. This may suggest that with active treatment, recovery from the major depressive episode is achieved as readily by patients with double depression as by those without chronic illness, but that more residual depressive symptoms persist among those with double depression. However, patients with double depression treated only by placebo-CM do not recover as readily. Results at follow-up should be most interesting, since previous studies have noted the greatest impact of double depression on subsequent course after recovery from the initial episode (38, 48).

Longer duration of the current episode predicted higher depression severity and a lower rate of complete response in the total sample but not the completer sample, suggesting that the influence of chronicity on recovery was greater among patients who did not complete treatment, most notably in the placebo-CM condition. This finding is consistent with many previous studies that have reported a negative relation between duration of illness and clinical outcome of psychotherapy (49–52), imipramine and other tricyclic antidepressants (34, 39, 53–55), and placebo (34, 56). Previous reports have indicated that acute onset of depression is a positive indicator of response to both tricyclic antidepressant treatment (7, 9, 45) and psychotherapy (33). In our study acute onset was associated with complete response among patients who completed imipramine treatment, and it predicted reduction in depression severity among patients treated with interpersonal psychotherapy, but only in the preliminary analyses within individual treatment conditions. Acute onset did not emerge as a significant predictor of differential treatment outcome in the main analyses. We therefore consider this to be only limited evidence supporting earlier findings.

Last, patients with higher expectation of improvement had a higher likelihood of recovery and lower level of depression severity across treatment conditions in both samples. Within individual treatment analyses, the negative influence of lower expectation of improvement appeared to occur among patients who received only placebo-CM or an incomplete course of imipramine (in the total sample only, not among completers of imipramine treatment). Low expectation of response to pharmacotherapy has been previously reported to predict attrition but not clinical outcome (57). In the psychotherapy literature, the relation of patient expectations to outcome has been generally positive (5, 6), consistent with these results. Other components of patient expectations and attitudes regarding treatment and depression remain to be explored. Since the pattern of findings for several patient predictors suggested a relation to outcome among patients who did not complete treatment, analyses of predictors of attrition are planned. Furthermore, the identification of potential patient predictors of long-term prognosis after initial treatment response will be of considerable clinical interest.

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# Prolactin and Cortisol Responses to *d*-Fenfluramine in Major Depression: Evidence for Diminished Responsivity of Central Serotonergic Function

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*Objective: Theoretically, d-fenfluramine should be a more selective serotonin (5-HT) challenge agent and has much greater clinical tolerance than the racemic compound that has previously been used. The authors' goal, therefore, was to look at 5-HT function in depression using the d isomer of fenfluramine as a probe. Method: They evaluated central 5-HT function in 23 patients with DSM-III-R-diagnosed major depression and 16 healthy control subjects. The depressed group included 10 men and 13 women; four were outpatients, two attended a day hospital facility, and 17 were inpatients. Subjects were cannulated at 8:30 a.m. after an overnight fast. After baseline samples were drawn, 30 mg of d-fenfluramine was administered orally and blood samples were drawn over the following 5-hour period for prolactin and cortisol estimation. Results: The plasma prolactin responses of the depressed patients were significantly lower than those of the control subjects. This blunting was not related to the severity of the depression but was significantly related to the patients' levels of state anxiety. Cortisol responses as well as prolactin responses were impaired in depression. High baseline cortisol levels were correlated with the severity of depression and the presence of weight loss. Conclusions: Overall, these findings indicate that there is diminished 5-HT responsivity in the depressed state.*

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Since the early 1960s, when impaired central monoamine activity was mooted as causative in depression, many attempts have been made to look at central serotonergic (5-HT) function using a neuroendocrine approach (1, 2). The most widely used neuroendocrine strategies have been the administration of the 5-HT precursors L-tryptophan (3, 4) and 5-hydroxytryptophan (5, 6) and the administration of agents that induce the release of 5-HT, such as fenfluramine (7–10), or agents that stimulate 5-HT receptors, such as buspirone (11) and ipsapirone (12).

Most of these tests have looked at plasma prolactin or cortisol concentrations or both following the 5-HT probe. There is a considerable body of evidence to suggest that 5-HT is involved in the release of prolactin centrally. Most 5-HT challenge agents increase prolactin secretion, and 5-HT antagonists decrease plasma prolactin concentrations (13). The evidence suggesting that 5-HT is involved in cortisol release by means of ACTH stimulation is less convincing (14), although many 5-HT agents, including fenfluramine, increase plasma cortisol levels (8) and ipsapirone, a selective 5-$HT_{1A}$ receptor agonist, brings about a substantial increase in plasma ACTH and cortisol levels that is selectively blocked by the 5-$HT_{1A}$ receptor antagonist pindolol (12, 15).

Plasma prolactin usually rises following intravenous administration of L-tryptophan (3), but it is unclear if this response is mediated through 5-HT pathways because pretreatment with the 5-HT-receptor-blocker cyproheptadine does not blunt the response (4). van Praag et al. (16) speculated that the response may result from alterations in dopamine metabolism because catecholamine turnover is decreased in the doses required to produce a prolactin response. Imura et al. (5) found that serum cortisol levels rose following oral administration of 5-hydroxytryptophan. This amino acid, however, is unreliable in increasing cortisol and prolactin levels in healthy subjects (6, 17) and may release catecholamines (18).

Buspirone, an azaspirodecanadione and 5-$HT_{1A}$ agonist, brings about a robust increase in plasma prolactin in normal subjects (11). This challenge agent has been criticized on the grounds that it is also active at dopamine sites and the prolactin response may well reflect alterations mediated by buspirone at this synapse (19).

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**TABLE 1. Characteristics of 23 Depressed Patients**

| Patient | Age (years) | Sex | Number of Previous Depressive Episodes | Family History of Depression | Hamilton Score | Newcastle Score |
|---|---|---|---|---|---|---|
| 1 | 30 | M | 8 | Positive | 22 | 4 |
| 2 | 61 | F | 4 | Negative | 27 | 5 |
| 3 | 29 | M | 0 | Positive | 23 | 5 |
| 4 | 18 | M | 0 | Positive | 18 | 0 |
| 5 | 22 | F | 1 | Positive | 22 | 1 |
| 6 | 54 | M | 2 | Positive | 25 | 3 |
| 7 | 39 | M | 8 | Positive | 17 | 6 |
| 8 | 38 | F | 3 | Positive | 23 | 2 |
| 9 | 35 | M | 1 | Positive | 22 | 4 |
| 10 | 50 | F | 3 | Negative | 22 | 6 |
| 11 | 64 | F | 1 | Positive | 32 | 7 |
| 12 | 38 | F | 1 | Negative | 20 | 6 |
| 13 | 47 | F | 2 | Negative | 21 | 4 |
| 14 | 19 | F | 1 | Negative | 17 | 2 |
| 15 | 30 | M | 1 | Positive | 21 | 5 |
| 16 | 29 | F | 1 | Negative | 23 | 6 |
| 17 | 32 | F | 10 | Negative | 30 | 6 |
| 18 | 34 | F | 3 | Positive | 20 | 5 |
| 19 | 52 | M | 0 | Negative | 19 | 5 |
| 20 | 35 | F | 2 | Positive | 21 | 8 |
| 21 | 57 | M | 1 | Negative | 28 | 8 |
| 22 | 42 | M | 0 | Positive | 34 | 7 |
| 23 | 32 | F | 6 | Negative | 26 | 8 |

Fenfluramine, a 5-HT-releasing agent and uptake inhibitor, causes a dose-dependent increase in prolactin in rats that is blocked by chemical or surgical lesioning of midbrain 5-HT neurones (20). Fenfluramine induces a dose-dependent increase in plasma prolactin levels in healthy human subjects (10) that is probably mediated through 5-HT mechanisms because pretreatment with cyproheptadine diminishes the response (7). Fenfluramine also causes a dose-dependent increase in ACTH and cortisol levels in normal subjects that is blunted by pretreatment with cyproheptadine (8).

*d,l*-Fenfluramine is not as selective a probe as originally thought; it causes the release of dopamine and noradrenaline as well as 5-HT (9). Studies in rats indicate that the *d*-isomer has a potent and specific effect at the 5-HT synapse (21) and that the catecholamine response is mediated by the *l*-isomer (22). Theoretically, therefore, *d*-fenfluramine should be a more selective 5-HT challenge agent than the racemic compound.

For this reason we decided to look at 5-HT function using the *d*-isomer of fenfluramine as a probe. To our knowledge, this is the first study using this challenge drug. We looked at responses in both healthy and depressed subjects.

## METHOD

Thirty-nine subjects participated in the study: 23 patients and 16 control subjects. All subjects were physically healthy, were not obese, and gave fully informed consent. Table 1 presents the characteristics of these patients.

The depressed group consisted of 10 men and 13 women between 18 and 64 years old (mean±SD=39.4±9.1). Four were outpatients, two attended a day hospital facility, and the remainder were inpatients. None had a diagnosis of substance abuse and none had a *DSM-III-R* axis II personality disorder.

Ten men and six women were included in the control group; their ages ranged from 22 to 42 years (35.68±3.2). None had a personal or family history of psychiatric disorder. All of the female subjects, except three women with postmenopausal depression, were tested within the first 10 days of the menstrual cycle.

For inclusion in the study patients had to fulfill *DSM-III-R* criteria for major depression. Eighteen of the patients were drug naive and five had been completely drug free for at least 6 weeks before the test. Severity of depression was rated by using the 17-item Hamilton Rating Scale for Depression (23); only those with scores of 17 or greater were included. The mean score was 24.3±7.5. "Endogenicity" was assessed by using the Newcastle Scale (24); the mean score on this scale was 4.9±0.20. Personality was assessed by using the Eysenck Personality Inventory (25).

Subjects, having fasted from midnight, began testing at 8:30–9:00 a.m. An intravenous cannula was inserted into a forearm vein and sealed with a rubber bung. The cannula was kept patent by flushing it with Heprinse (0.5 ml, 50 units heparin) after samples of blood were taken and the first 2 ml extracted at each time point was discarded. The subject relaxed for 15 minutes and serial blood samples were then taken 15 minutes before, at 0 minutes, and 60, 120, 180, 240, and 300 minutes after administration of *d*-fenfluramine for estimation of prolactin and cortisol levels; 30 mg of *d*-fenfluramine was administered at 0 minutes. Subjects remained in a supine position throughout the procedure and were served a standard light breakfast about 1 hour after medication administration.

Approximately 8 ml of blood was collected into vacuum lithium heparin-treated tubes and immediately centrifuged and put on ice. Analysis was carried out in batches and blind to subjects' status. Prolactin levels were measured by standard fluroimmunoassay (26) using a commercial kit; intra- and interassay coefficients of variation were 2% and 5.7%, respectively, at about 100 mU/liter, and the sensitivity was 1.5 mU/liter. Cortisol levels were measured by radioimmunoassay according to the method of Pash et al. (27); intra- and interassay coefficients of variation were 2.2% and 3.5%, respectively, at about 300 nmol/liter, and the sensitivity was 3–5 nmol/liter.

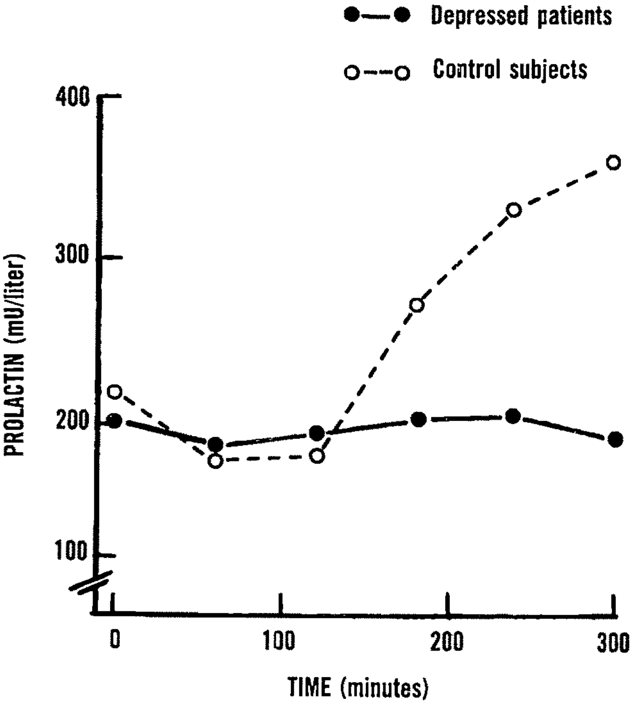
The hormonal responses of the depressed male and female patients and control subjects were compared over time. Three-way analysis of variance (ANOVA) and post hoc tests were applied to these comparisons. Analysis of covariance was used to analyze responses when baseline levels were significantly different. To analyze differences in response within the depressed group, delta values (the difference between baseline hormone levels and maximum increase after *d*-fenfluramine administration) were compared by using Student's t tests. Chi-square tests and the Pearson product moment correlation coefficient were used when appropriate. All results are expressed as mean±standard deviation. Data were analyzed by means of Statgraphics (28).

## RESULTS

### *Prolactin*

A repeated-measures three-way ANOVA comparing prolactin responses to *d*-fenfluramine over the six time points (mean baseline values) between depressed and control groups and between men and women yielded a significant Group by Time interaction (F=3.91, df=5, 229, p=0.002) (figure 1). Tukey's post hoc tests showed this difference to be significant 300 minutes after administration of *d*-fenfluramine only (p<0.05). A main effect for sex just failed to reach significance (F=3.63, df=1, 232, p=0.58), and there was no significant interaction effect for this variable. Although there was a tendency for baseline prolactin levels to be lower in the depressed group (202.00±105.75 mU/liter) than in healthy control subjects (222.00±125.63 mU/liter), this difference was not significant (p=0.79).

FIGURE 1. Changes in Plasma Prolactin Levels Following Administration of 30 mg of *d*-Fenfluramine in 23 Depressed Patients and 16 Healthy Control Subjects



When patients were classified on the basis of their symptoms by using the Newcastle Scale scores into those with endogenous and nonendogenous symptoms, the eight patients with nonendogenous (neurotic) symptoms showed a greater degree of blunting than did the 15 patients with endogenous symptoms. The mean delta prolactin in the nonendogenous group was 21.5±19.58 mU/liter, compared with 76.66±70.52 mU/liter in the endogenous group (t=2.14, df=21, p=0.04). Patients with blunted responses had higher scores on the anxiety-related variables of the Hamilton depression scale (t=4.82, df=21, p<0.01) than did those without blunted responses, but the two groups were not distinguished by their overall Hamilton depression scores. Neuroticism scores, assessed by the Eysenck Personality Inventory, did not distinguish the patients with and without blunting (t=0.68, df=21, p=0.49).

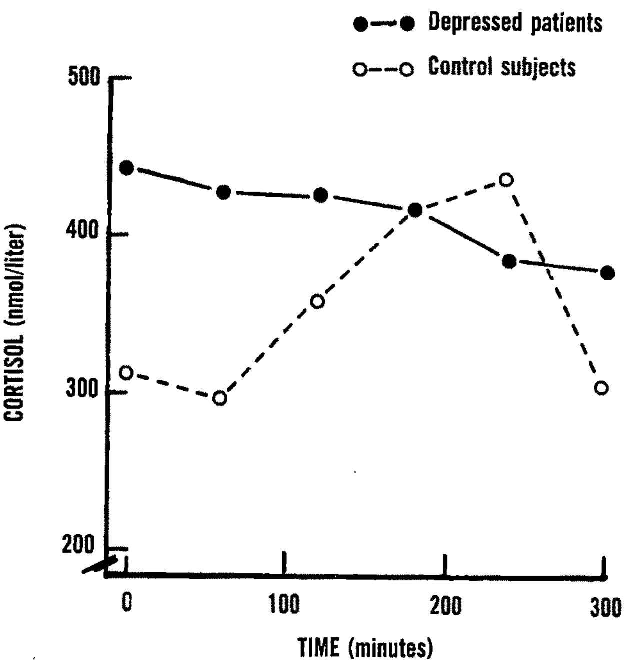
Weight loss, a core endogenous variable, was significantly associated with a nonblunted rather than a blunted response ($\chi^2$=4.97, df=1, p=0.025, chi-square with Yates's correction). The mean±SD delta prolactin in the patients with weight loss was 93.4±67.8 mU/liter; in those without weight loss it was 22.8±33.0 mU/liter (t=3.3, df=21, p=0.003).

Blunting of response was not associated with age, sex, past personal or family history of depression, or previous exposure to psychotropic medication. Neither was blunting associated with the presence of suicidal ideation or a history of suicidal attempts.

### *Cortisol*

Like the analysis of prolactin, a three-way ANOVA comparing cortisol responses over time showed a significant Group by Time interaction (F=7.24, df=5, 229, p<0.001) (figure 2). Baseline values of patients and control subjects differed significantly (t=3.56,

**FIGURE 2. Changes in Plasma Cortisol Levels Following Administration of 30 mg of *d*-Fenfluramine in 23 Depressed Patients and 16 Healthy Control Subjects**



df=37, p= 0.001), but covarying for this did not alter the significance (F=7.88, df=5, 229, p<0.001). The plasma cortisol values of all subjects dropped steadily over the first hour, but there was no difference between depressed and control subjects in the cortisol decrease from 15 minutes before to 60 minutes after *d*-fenfluramine administration. There was no significant effect for sex.

High baseline cortisol levels were significantly correlated with the severity of depression according to the Hamilton depression scale scores (r=0.97, p<0.001) and with the presence of weight loss (r=0.85, p<0.001). Blunting of cortisol responses, however, did not distinguish the patients with endogenous symptoms from those with nonendogenous symptoms. Neither could blunting be explained in terms of patients' age, sex, family history, past history, or symptoms such as weight loss or suicidal ideation.

Eleven of the 23 patients had blunted cortisol and blunted prolactin responses, but there was no substantial overlap between the two groups (i.e., blunting of one response did not increase the likelihood of blunting in the other).

## DISCUSSION

*d*-Fenfluramine brought about marked elevations in serum cortisol and prolactin in healthy control subjects. This response was attenuated in our depressed patients, suggesting abnormalities in central 5-HT function in depression.

### *Prolactin*

Siever's group (29) first described a diminished prolactin response to *d,l*-fenfluramine in acutely depressed patients compared with control subjects, but they did not look at related clinical variables. More recently, Coccaro et al. (30) found similar responses in patients with histories of major depression regardless of whether they were currently depressed. Our findings are in agreement with this group to the extent that we found no relationship between the severity of the depression and the prolactin response to *d*-fenfluramine but limited by the fact that we tested only patients who were currently depressed. In contrast, another group (31) suggested that this response may be a good marker of the grade of "endogenicity" of depressive disorder—that responses are most blunted at one extreme of a hypothetical spectrum from melancholia through more neurotic-type depression to dysthymia, where responses are least blunted. This association between severity of depression and blunting of the prolactin response to *d,l*-fenfluramine has also been found by Mitchell and Smythe (32) in a recent study in which they found no overall difference for change in prolactin in a group of 27 depressed patients but a significantly reduced response in those with endogenous depression. Our results are in apparent contradiction to theirs. When our patients with similar Hamilton depression scores were divided into those with endogenous and nonendogenous symptoms by using the Newcastle Scale, those with nonendogenous features, especially severe anxiety, were most likely to have blunted responses. The association was with state rather than trait anxiety because the groups did not differ on anxiety variables on the personality questionnaire.

In two other studies (33, 34) the prolactin response to *d,l*-fenfluramine was unable to distinguish patients from control subjects. One of these (33) found that eight depressed patients had less marked responses than eight control subjects; because of the small number of subjects, however, these conclusions may reflect a type II error. The other study (34) used subjects with bipolar as well as unipolar depression, and neither took into account the menstrual status of the female subjects.

Impaired prolactin response to intravenous L-tryptophan has also been described in depressed individuals (35, 36). Interestingly, as in the present study, Cowen and Charig (35) found that depressed individuals with marked weight loss (more than 10 lb) were less likely to show blunting of response than individuals who had not lost weight. Neither did they find any significant correlation between suicidal score or Hamilton score and change in prolactin; they concluded that it was the epiphenomenon of weight loss that altered the 5-HT response in this subgroup. Only one study of the response of prolactin to *d,l*-fenfluramine (32) has looked at weight loss and found no effect for it. There is a substantial amount of evidence to suggest that obese subjects have subnormal prolactin responses to *d,l*-fenfluramine (37, 38), and for this reason they are excluded from most studies. It may be that severe weight loss induces responses in the opposite direction, giving a relatively enhanced prolactin response to depressed individuals who have lost weight. This hypothesis is supported by a markedly enhanced prolactin response to tryptophan in women following a 3-week weight-reducing diet (39). In one study of obese women (40) the plasma concentration of *d,l*-fenfluramine was highly correlated with weight loss: those individuals with the greatest weight reduction had the highest blood levels of fenfluramine. Because we did not look at plasma *d*-fenfluramine concentrations, we do not know if our finding is due to altered absorption of this drug and suggest that this may be a useful variable to look at in further studies using this probe.

As stated in the Method section, we tested premenopausal women in the early follicular stage of the menstrual cycle. Our findings indicate that prolactin responses to *d*-fenfluramine vary widely throughout the menstrual cycle of healthy women, paralleling estrogen fluctuations; the response in the luteal phase is much greater than that in the early follicular phase (41). Explanations for this are suggested by the findings of rat studies indicating that estrogen and progesterone up-regulate 5-HT receptors (42, 43). It may be that rising levels of gonadal steroids following ovulation induce similar alterations in central 5-HT function in women. No previous studies have controlled for this variable.

Finally, the trend for prolactin values to be higher initially in the healthy control subjects than in the depressed group is interesting in the light of other findings of significantly lower plasma prolactin values in depression (29, 30, 32). In our study, this tendency did not reach statistical significance. Moreover, prolactin levels dropped by greater amounts in healthy subjects (68.00±25.65 mU/liter) than in depressed subjects (44.27±11.53 mU/liter). Since this drop is highly unlikely to be mediated by fenfluramine on either theoretical or pharmacokinetic grounds (peak *d*-fenfluramine plasma levels occur 2–4 hours after ingestion), it may represent a central response to stress that is less marked in depressive illness (i.e., healthy subjects show a greater increase in prolactin levels as a result of cannulation than do depressed patients).

### *Cortisol*

We found that the response to cortisol in our depressed patients was significantly worse than that of the healthy control subjects, and that this impaired response was not associated with specific aspects of the patients' histories or mental states. As in previous studies, a relationship between the severity of depression and baseline cortisol levels was established, as was the relationship with weight loss (6, 32, 44). This association between melancholic depression and abnormal adrenocortical function is well established (45, 46). Administration of corticotropin-releasing factor results in less release of ACTH in depressed patients than in control subjects with no difference in cortisol secretion (47, 48), and the adrenal cortex is hyperresponsive to exogenous ACTH in depression (49).

Meltzer et al. (50) reported an enhanced cortisol response to oral 5-HT in depression and an association with suicidal thoughts. They concluded that 5-HT receptors were up-regulated secondary to diminished availability of 5-HT in depressive illness. Studies on cortisol responses to *d,l*-fenfluramine in depression have been contradictory: two groups (32, 34) found normal responses, and one (33) found that blunted cortisol responses distinguished depressed patients from control subjects. The two former studies included patients with bipolar disorder, and the patients had been drug-free for only a minimum period of 3 weeks in one study (34) and 2 weeks in the other (32). Our results and those of previous studies are limited by the fact that cortisol rather than ACTH was measured.

### *d-Fenfluramine Versus d,l-Fenfluramine as a Probe*

Although reference is made to unpleasant side effects in only one previous study using *d,l*-fenfluramine as a challenge drug (51), we found these side effects to be intolerable in our work with this drug. In an unpublished pilot study, we found that these side effects included dysphoria, depersonalization, rigors, abdominal distension and cramps, constipation, and anxiety and were experienced to a greater or lesser extent by all six healthy volunteers who took part in this study. *d*-Fenfluramine, however, produced mild sedation in four subjects and possible headache the following day in two but overall was very well tolerated and had almost no spontaneously reported ill effects.

*d,l*-Fenfluramine is a nonspecific 5-HT agent that can be used to assess presynaptic function by its releasing and uptake-inhibition properties and postsynaptic function by stimulation of all 5-HT receptor subtypes by the released 5-HT (9). The *d*-isomer, although "cleaner" pharmacologically, is also limited by the fact that *d*-fenfluramine assesses "net" 5-HT activity. One can only speculate at this stage about whether the 5-HT alterations in depression result from abnormalities in the presynaptic or postsynaptic regions and which 5-HT receptor subtypes are involved in mediating these responses. Clearly, further studies are needed that pretreat subjects with selective 5-HT receptor antagonists to elucidate which receptors mediate the 5-HT endocrine responses. Studies using ipsapirone (12, 15) suggested that it is the 5-$HT_{1A}$ receptor that is involved in ACTH and cortisol release. Given that the subgroups of nonresponders were different for both prolactin and cortisol, it is likely that different receptors are involved in the release of both.

## CONCLUSIONS

We found that prolactin and cortisol responses to *d*-fenfluramine were significantly impaired in patients with major depression compared with healthy control subjects and that this blunting was not related to the severity of the depression. Our findings differ in some respects from previous studies, perhaps because the novel probe used in this study is more selective for 5-HT and less likely to induce a stress response than those used in previous studies.

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## New Policy for References

Effective with the September 1991 issue, *The American Journal of Psychiatry* will institute a policy of listing the names of all authors of work cited in references. Authors of submitted manuscripts and letters to the Editor must include the surnames and initials of all authors in references. The use of "et al." is no longer acceptable.

# Correlates of Psychiatric Distress Among Wives of Hemophilic Men With and Without HIV Infection

**Mary Amanda Dew, Ph.D., Margaret V. Ragni, M.D., and Pamela Nimorwicz, M.S.W.**

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Objective: *The authors' objectives were 1) to examine symptoms of depression, anxiety, and anger-hostility among the wives of men with hemophilia, a major risk group for AIDS, and 2) to identify psychosocial characteristics of the women and/or their husbands that were associated with elevated distress in the women.* Method: *Thirty-six women married to men with hemophilia were studied; the husbands of 17 of these women were HIV-seropositive. The men were drawn from the population of adults with hemophilia residing in a 24-county region of western Pennsylvania. Measures of wives' psychiatric symptoms were obtained, as were measures in three psychosocial domains: predispositional sociodemographic characteristics, psychosocial stressors, and husbands' strategies for coping.* Results: *The psychiatric symptoms of the women did not differ as a function of their husbands' serostatus or across subgroups defined according to stages of HIV infection or clinical severity of hemophilia. Instead, other factors—perceptions of personal risk of AIDS, husbands' use of particular coping styles with respect to HIV infection, and the experience of other life events—were the principal correlates of psychiatric distress.* Conclusions: *HIV infection acted primarily as an indirect source of stress for these women, mediated by other psychosocial characteristics of both the women and their HIV-seropositive husbands. Mental health interventions for caregivers of HIV-seropositive individuals should target the identified psychosocial correlates of psychiatric distress.*

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A dramatic consequence of infection by HIV is its deleterious effect on mental health. In addition to its potential for neuropsychological complications (1), HIV infection engenders a constellation of interrelated psychosocial stressors. The emotional toll of protracted coping with this chronically stressful situation has received increasing attention in major groups of persons at risk for AIDS, including homosexual men (2–4) and men with hemophilia (5).

Qualitative accounts emphasize the need to consider the partners of HIV-seropositive individuals when evaluating the mental health consequences of HIV-related stress (6, 7). The emotional well-being of the partner of the afflicted individual may ultimately play an important role in the individual's health (8). Indeed, previous work with HIV-seropositive men with hemophilia (5) indicates that emotional and practical support from their wives was a critical factor related to the men's psychiatric distress levels. Nevertheless, there has been little systematic examination in the literature of these partners of the well-being of partners of HIV-seropositive individuals and the ability to provide such support.

A burgeoning literature on caregiving to individuals with a variety of other chronic conditions (9, 10) suggests that caregiving in the context of HIV infection may exact high emotional costs. The psychological sequelae noted frequently in this literature include, most notably, depression and demoralization (10), but symptoms of anxiety and elevated anger and hostility levels have been observed as well (9, 10). Conceptual models of the process whereby the illness of a patient produces an emotional burden on the caregiver emphasize the need to incorporate both patient factors (e.g., mode of coping with the illness) and caregiver characteristics (e.g., demographic characteristics and supportive resources) into empirical evaluations of this stress process (9).

The present study considered such factors in an examination of the mental health of wives of hemophilic men. Many of these men were HIV seropositive. Approximately 50%–65% of men with hemophilia in the United States are infected with HIV due to exposure to

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**TABLE 1. Background Characteristics of HIV-Seropositive and HIV-Seronegative Men With Hemophilia and Their Wives and Psychiatric Symptoms of the Wives**

| | Husband Seropositive | | | Husband Seronegative | | | Analysis | |
|---|---|---|---|---|---|---|---|---|
| Item | Total (N=17) | Group A[a] (N=10) | Group B[a] (N=7) | Total (N=19) | Group C[a] (N=10) | Group D[a] (N=9) | HIV Seropositive Versus HIV Seronegative[b] | Four-Group Comparison[c] |
| Background characteristics | | | | | | | | |
| Couples | | | | | | | | |
| Family income $20,000 or more | 7[d] | 3[d] | 4 | 14 | 6 | 8 | $\chi^2=2.16$ | $\chi^2=5.82$ |
| Blue-collar worker | 8 | 6 | 2 | 8 | 4 | 4 | $\chi^2=0.00$ | $\chi^2=1.77$ |
| White | 17 | 10 | 7 | 19 | 10 | 9 | — | — |
| Married for 10 years or less | 13 | 8 | 5 | 6[d] | 3[d] | 3 | $\chi^2=4.93$[e] | $\chi^2=6.68$[f] |
| Children in the home | 10 | 5 | 5 | 5 | 2 | 3 | $\chi^2=2.68$ | $\chi^2=5.03$ |
| Wives | | | | | | | | |
| Younger than 35 years old | 11 | 6 | 5 | 6 | 4 | 2 | $\chi^2=2.73$ | $\chi^2=4.77$ |
| High school education or less | 7[d] | 5 | 2[d] | 8[d] | 5 | 3[d] | $\chi^2=0.00$ | $\chi^2=0.71$ |
| Unemployed | 9 | 6 | 3 | 9 | 5 | 4 | $\chi^2=0.11$ | $\chi^2=0.65$ |
| Husbands | | | | | | | | |
| Younger than 35 years old | 10 | 6 | 4 | 6 | 4 | 2 | $\chi^2=1.71$ | $\chi^2=3.32$ |
| High school education or less | 5 | 4 | 1 | 8 | 4 | 4 | $\chi^2=0.20$ | $\chi^2=1.85$ |
| Unemployed | 7 | 4 | 3 | 8 | 6 | 2 | $\chi^2=0.00$ | $\chi^2=2.80$ |
| Psychiatric symptoms in wives[g] | | | | | | | | |
| SCL-90 depression score | | | | | | | | |
| Mean | 0.33 | 0.35 | 0.31 | 0.27 | 0.23 | 0.32 | t=0.13 | F=0.10 |
| SD | 0.86 | 0.98 | 0.82 | 0.78 | 0.76 | 0.84 | | |
| SCL-90 anxiety score | | | | | | | | |
| Mean | 0.17 | 0.19 | 0.16 | 0.20 | 0.25 | 0.16 | t=006 | F=0.12 |
| SD | 0.49 | 0.50 | 0.63 | 0.52 | 0.76 | 0.42 | | |
| SCL-90 anger-hostility score | | | | | | | | |
| Mean | 0.21 | 0.21 | 0.22 | 0.14 | 0.08 | 0.25 | t=0.54 | F=0.79 |
| SD | 0.54 | 0.63 | 0.55 | 0.48 | 0.38 | 0.42 | | |

[a] Group A consisted of women whose husbands were HIV seropositive, met CDC criteria for stage IV infection or had a CD4% less than 20%, and had mild to severe hemophilia. Group B consisted of women whose husbands were HIV seropositive, had both CDC stage II or III infection and CD4% of at least 20%, and had moderate to severe hemophilia. Group C consisted of women whose husbands were HIV seronegative and had moderate to severe hemophilia. Group D consisted of women whose husbands were HIV seronegative and had mild hemophilia and minimal use of blood products.

[b] Chi-square values computed with Yates' correction; df=1. For the t values, df=34.

[c] Chi-square values computed with Yates' correction; df=3. For the F values, df=3, 33. Values should be interpreted cautiously because of small frequencies (fewer than five subjects).

[d] Data were not available for one subject/couple.

[e] $p<0.05$.

[f] $p<0.07$.

[g] 0=not at all, 4=extremely distressed. Data were log-transformed to reduce skewness. Group means have been reconverted from the log scale to the original (raw-score) scale to facilitate interpretation.

contaminated blood products in the early 1980s (11). AIDS is the leading cause of death in this population. The wives of HIV-seropositive hemophilic men must cope not only with their husbands' health concerns but with other difficult issues, such as the couple's concerns and frustrations regarding sexual precautions. These women must also reconcile themselves to the fact that taking safe sexual precautions will render them unable to have additional (or, perhaps, any) children parented by their husbands.

Our study had two goals: 1) to examine patterns of women's psychological distress as a function of whether their husbands were HIV seropositive as well as according to their husbands' stage of infection and 2) to identify psychosocial characteristics of the women and/or their husbands that are associated with elevated distress among these women.

## METHOD

### *Subjects*

Seventy-five men, representing 73% of the adult (18 years old or older) men with hemophilia in a 24-county region of western Pennsylvania, were interviewed in our original study (5). The wives of 37 (34%) of the 44 men who were married or living with a partner completed paper-and-pencil booklets during their husbands' interviews. Because one woman (whose husband was HIV seronegative) was an extreme outlier on distributions of all variables and was excluded from analyses, 36 women were considered. The husbands of 17 of these women were HIV seropositive; one of these 17 women was herself HIV seropositive. According to information obtained from the husbands (e.g., demographic charac-

**TABLE 2. Associations Between Psychiatric Symptoms and Psychosocial Characteristics in 36 Women Whose Husbands Had Hemophilia[a]**

| | Psychiatric Symptoms[b] | | | | | |
|---|---|---|---|---|---|---|
| | Depression | | Anxiety | | Anger-Hostility | |
| Psychosocial Variable | Gross | Net | Gross | Net | Gross | Net |
| Predispositional | | | | | | |
| Wife's age | 0.22 | 0.20 | 0.02 | –0.02 | –0.14 | 0.06 |
| Wife's education | 0.11 | 0.01 | 0.04 | –0.06 | 0.09 | –0.07 |
| Wife's employment status[c] | 0.38[d] | 0.42[d] | 0.33[d] | 0.31[e] | 0.28[e] | 0.36[e] |
| Family income[c] | 0.07 | 0.04 | 0.06 | 0.09 | 0.05 | 0.04 |
| Family occupational status[c] | 0.06 | 0.08 | 0.04 | 0.11 | –0.14 | –0.16 |
| Positive mental health history | 0.14 | –0.02 | 0.18 | 0.11 | –0.13 | –0.27 |
| Stressors | | | | | | |
| Marital strain—wife | 0.39[d] | 0.34 | 0.37[d] | 0.30 | 0.43[d] | 0.36 |
| Marital strain—husband | 0.28 | 0.04 | 0.26 | 0.01 | 0.34[d] | 0.03 |
| Wife's risk of AIDS | 0.36[d] | 0.43[d] | 0.34[d] | 0.49[f] | 0.32[d] | 0.32[e] |
| Life events involving loss | 0.35[d] | 0.34[d] | 0.37[d] | 0.36[d] | 0.39[d] | 0.36[d] |
| Husband's strategies for coping | | | | | | |
| With hemorrhages | | | | | | |
| Active cognitive | 0.11 | –0.11 | 0.17 | –0.19 | 0.09 | 0.04 |
| Active behavioral | 0.09 | 0.10 | 0.24 | 0.23 | 0.04 | 0.01 |
| Avoidance | 0.24 | 0.13 | 0.35[d] | 0.28 | 0.23 | 0.16 |
| With HIV and AIDS threat | | | | | | |
| Active cognitive | 0.16 | 0.03 | 0.19 | 0.32 | 0.04 | –0.10 |
| Active behavioral | 0.15 | 0.19 | 0.00 | –0.22 | 0.10 | 0.12 |
| Avoidance | 0.31[e] | 0.35 | 0.16 | 0.13 | 0.28 | 0.25 |

[a] Only cases with complete data (table 1) were used for the analysis of predispositional variables. Analyses for stressors and for coping strategies were based on N=36.

[b] Gross effects are indicated by zero-order correlation coefficients. Net effects are standardized regression coefficients (main effects) controlling for all other variables in a given domain.

[c] Higher scores indicate employment, as opposed to unemployment, higher income, and blue collar as opposed to white collar status, respectively.

[d] $p<0.05$.

[e] $p<0.07$.

[f] $p<0.01$.

teristics, described later in the paper), the 36 women and their husbands did not differ from the couples who did not participate in the study. Informed consent was obtained from both husbands and wives.

We categorized the women into four subgroups on the basis of clinical and immunologic evidence related to their husbands' HIV infection as well as the clinical severity of their husbands' hemophilia. (In general, the more severe the hemophilia, the more likely the men had been exposed to HIV.)

Group A consisted of 10 women (including the one HIV-seropositive woman) whose husbands were HIV seropositive as determined by ELISA with Western blot confirmation (12). The husbands of these women either met Centers for Disease Control (CDC) criteria (13) for stage IV infection (AIDS and/or two or more persistent constitutional symptoms) or had a severely depressed percentage (less than 20%) of CD4 cells of the total lymphocyte cell count (CD4%), reflecting compromised immunologic status. (The mean±SD CD4% was 12.1%±4.2%.) Nine husbands had moderate to severe hemophilia (i.e., less than 5% coagulant activity in the blood); one had mild hemophilia.

Group B consisted of seven women whose husbands were HIV seropositive and had moderate to severe hemophilia. These men were characterized by CDC stage II or III infection (i.e., either asymptomatic or with generalized lymphadenopathy syndrome but no other symptoms) and a CD4% of at least 20%. (The mean CD4% for husbands in group B was 24.9%±3.9%.)

Group C consisted of 10 women whose husbands were HIV seronegative. These men had moderate to severe hemophilia and thus, like the HIV-seropositive men, had been at risk for infection during the early 1980s.

Group D included the remaining nine women whose husbands who were HIV seronegative and who, by virtue of their mild hemophilia and minimal use of blood products, had been consistently at low risk for infection.

The upper section of table 1 presents background characteristics of the women and their husbands according to the husband's infection status as well as by assignment to the four study subgroups. The effects of the duration of HIV infection and of the time since diagnosis among the husbands in groups A and B cannot be evaluated in subsequent analyses: duration of infection, determined retrospectively from blood samples collected annually since 1977, was very similar for groups A and B (mean±SD for group A, 5.2±1.5 years; for group B, 5.4±0.6 years). All but two men had been infected for more than 4.5 years. Almost all of the men had known of their infection status for approximately the same length of time (group A, 2.0±0.3 years; group B, 2.1±0.3 years).

### *Procedure*

Psychiatric symptoms were assessed by using the depression, anxiety, and anger-hostility subscales of the Symptom Checklist-90 (SCL-90) (14), a self-report checklist measuring current subclinical levels of disturbance (0=not at all, 4=extremely distressed). Each subscale score was formed by averaging the relevant items (scored in their original units). Internal consistency reliability for the entire study group (Cronbach's alpha) was 0.94, 0.91, and 0.84 for the depression, anxiety, and anger-hostility subscales, respectively. Subscale scores were log-transformed before analyses to reduce skewness in their distributions.

Three domains of psychosocial factors were examined: predispositional characteristics, psychosocial stressors, and husbands' strategies for coping.

*Predispositional characteristics.* In addition to the demographic profile (table 1), we determined the women's histories of sustained periods of depressive and/or anxiety-related mood before their husbands' seroconversion with two lead questions from the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (15). For depressive mood, the question was, "Have you ever had a period lasting 2 weeks or longer when you were feeling depressed or down most of the day nearly every day?" The anxiety question was similar: "Have you ever had a period lasting 2 weeks or longer when you were feeling nervous or anxious and worrying most of the time?"

*Psychosocial stressors.* First, to measure marital strain each member of the couple independently completed a 20-item questionnaire (5, 16). A marital strain index for the wives was created by averaging the items (alpha=0.96); a similar index was created for husbands (alpha=0.90). For each index, we defined high marital strain as scoring in the upper half (most strain) of the distribution. Second, wives were asked whether their risk of AIDS was lower, the same, or higher than that of other individuals. Third, the number of stressful life events involving personal loss (e.g., death of a family member) (17) occurring in the 6 months before interview was the sum of items the husband endorsed on a shortened version of the Psychiatric Epidemiology Research Interview (PERI) Life Events Scale, which has been validated in large community samples (18).

*Husbands' strategies for coping.* The coping styles of the husbands were assessed with the Coping Checklist (19). Men completed this checklist first concerning coping with a hemorrhage occurring during the past year, an event for which men were likely to have established a personal, routine approach.

Our choice of a hemorrhage as one context in which to evaluate coping permitted a variety of responses regarding the men's actions or lack thereof. Many hemorrhages—especially the common internal hemorrhages into joints—do not require immediate administration of coagulation factor for survival, thus allowing a range of other initial responses to be made (5).

The men completed the Coping Checklist a second time regarding strategies they used during the month before interview to cope with issues related to HIV infection and AIDS.

For each of the two coping areas, we created three indexes (19). Active cognitive coping was the sum of positive responses to any of five items (e.g., drew on past experiences). Active behavioral coping was the sum of positive responses to any of eight items (e.g., consulted a health professional). Avoidance coping was the sum of positive responses to five items (for hemorrhages) or eight items (for HIV infection) (e.g., smoked more to reduce tension). These indexes have been validated and used in a number of investigations (19), reviewed by Cohen (20).

## RESULTS

We first examined the women's symptom levels as a function of their husbands' serostatus as well as according to their membership in the four study subgroups (lower section of table 1). There were no sizable or significant symptom differences according to husband's serostatus or across the four study subgroups. Furthermore, the women's mean symptom levels were virtually identical to those reported for a normative female community sample (14), indicating that there is no evidence of a general heightening of distress across the entire study group.

We also determined the number of women who demonstrated clinically meaningful distress levels. According to Derogatis (14), women scoring more than one standard deviation above the mean for the normative female community sample on the SCL-90 subscales are considered highly symptomatic. Five (29%) of the 17 women whose husbands were HIV seropositive exceeded this cutoff point on the depression subscale, four (24%) on the anxiety subscale, and three (18%) on the anger-hostility subscale. The numbers in the HIV-seronegative group were very similar: seven (37%) of these 19 women exceeded this cutoff point on the depression subscale, four (21%) on the anxiety subscale, and five (26%) on the anger-hostility subscale. The numbers of highly symptomatic women whose husbands were HIV-seropositive did not differ sizably or significantly from the numbers of highly symptomatic women married to HIV-seronegative men on these subscales (for depression, $\chi^2$=0.02, df=1; for anxiety, $\chi^2$=0.04, df=1; for anger-hostility, $\chi^2$=0.03, df=1).

Given the lack of effects of their husbands' HIV status on the women's current psychiatric symptoms, what accounts for observed variability in symptom scores? As shown in table 2, zero-order correlation coefficients, indicators of *gross* associations of psychosocial characteristics with symptom outcomes, suggest that variables in the stressor domain were most strongly related to symptoms. Thus, greater degrees of stress (e.g., the wife's perception of greater marital strain, her perception that she was at risk for AIDS, and the experience of a greater number of loss events) were correlated with elevated symptoms of depression, anxiety, and anger-hostility.

The *net* effects of each psychosocial characteristic, controlling for other characteristics in a given domain, are also shown in table 2. These coefficients were determined by regressing each outcome mental health variable on all of the variables within a given domain. They indicate that, first, the only predispositional variable related to symptoms was employment status (upper section of table 2): employed women were more symptomatic. (HIV status exerted only a small, nonsignificant effect in this and subsequent regressions. It also did not alter the impact of [i.e., interact with] any predispositional characteristic.)

The midsection of table 2 shows that the most important psychosocial stressors were the wife's perception that she was at risk of AIDS and the experience of a greater number of loss events. It is noteworthy that the husband's HIV status did not interact with these variables; for example, the impact of a woman's perceptions of her risk of AIDS on her symptom levels was not influenced by whether her husband was HIV seropositive. Similarly, the effect of loss events on symptoms was not moderated by the man's HIV status.

The lower section of table 2 presents the gross and net effects for the husbands' strategies for coping. The regression analysis indicated that the husbands' strategies for coping were not, by themselves, linked to their wives' symptoms. However, two important interaction effects emerged between HIV status and the coping measures. First, the husbands' use of active cognitive coping with respect to HIV was linked to higher symptoms among their wives, but only among HIV-seropositive couples (for depression, $b=3.77$, $p<0.001$; for anxiety, $b=3.36$, $p<0.01$; for anger-hostility, $b=4.15$; $p<0.01$). Second, among HIV-seropositive couples (but not among their HIV-seronegative counterparts), failure by the husbands to use avoidance coping tactics regarding HIV was related to higher symptoms of depression ($b=-2.90$, $p<0.01$) and anger-hostility ($b=-2.70$, $p<0.05$) among their wives.

Finally, to assess whether the proportion of women with clinically significant symptom levels increased with the total number of individually significant psychosocial characteristics of the 36 couples, a test for a linear trend in proportions was performed (21). This test compared women who were highly symptomatic on one or more of the subscales (i.e., those exceeding the Derogatis cutoff points) with women scoring below the cutoff points on all three subscales.

A single "dose" variable was created by determining how many of five characteristics women possessed. These five characteristics, found to be most strongly related to wives' mental health in the regression analyses, were whether 1) the wife was employed, 2) the wife perceived herself at high risk of AIDS, 3) the wife and the husband experienced at least one recent life event involving personal loss, 4) the husband used active cognitive coping with respect to HIV infection (defined as scoring above the median on this measure), and 5) the husband failed to use avoidance strategies to cope with the threat of HIV and AIDS (defined as scoring below the median).

Results revealed a dose effect ($Z=5.42$, $p<0.001$). Among the 11 women with none or one of these psychosocial factors present, two (18%) had clinically significant distress; among the 22 women with two to three factors, 10 (45%) had significant distress; of the three women with four to five factors, two (67%) had significant distress. Although these data must be interpreted with caution appropriate to the small study group, they suggest that as the number of psychosocial contributory factors increases, the likelihood of experiencing elevated psychiatric distress increases as well.

## DISCUSSION

This study extends previous work on the mental health impact of HIV infection on wives of individuals in a major heterosexual risk group for AIDS. Surprisingly, we found no sizable or significant differences in the wives' psychiatric symptoms as a function of their husbands' serostatus or across subgroups defined according to clinical and immunologic evidence regarding the husbands' infection as well as the clinical severity of their hemophilia. In addition, the women's mean symptom levels were virtually identical to those reported for a normative community sample. The low symptom levels among all women attest to their strength in coping both with the stresses of their husbands' hemophilia and their husbands' HIV serostatus.

Do these results indicate that issues related to HIV infection and AIDS were unimportant for these women? We think not. The psychosocial variables that were related to women's symptoms can be viewed, in large part, as indirect indicators of HIV-related issues. Consider first the finding that being employed was associated with elevated psychiatric distress levels. Although adverse effects of employment among women have sometimes been noted (22), we suggest that the association may have emerged in our study group because many women—especially those whose husbands were HIV seropositive—appeared to feel that they should have been at home to offer emotional and practical support to their husbands. A number of women stated that they had quit their jobs out of concern for their husbands' health. Additional comments reflected frequent feelings of tension regarding their husbands' health and their own employment. For example, one woman whose husband had AIDS said that he "doesn't want me to go anywhere without him . . . as if he doesn't want to be alone." Another woman said that she had taken off large blocks of time from her job to be with her husband.

Results concerning one of our psychosocial stressor variables also suggest the importance of HIV-related issues. A woman's perception that she herself was at elevated risk of AIDS was strongly related to elevated psychiatric distress levels. It is critical to note that these perceptions operated independently of the husband's serostatus: women who perceived themselves at higher risk of AIDS than other people were more symptomatic regardless of whether their husbands were HIV seropositive. Much as other studies have found that objective information regarding presence or absence of HIV-related symptoms is not enough to alleviate individuals' distress over perceived symptoms (23, 24), we too have found that these women's perceptions of their own risk of infection and AIDS were not affected by the objective reality of their husbands' serostatus.

The couple's experience of recent life events involving loss was also an important stress variable. Our data underscore the potential for deleterious mental health effects when multiple stressful events occur at the same time (5).

The associations of wives' mental health with husbands' strategies for coping were perhaps the most intriguing results of all. It has long been accepted clinically that, although useful under certain circumstances, avoidance strategies for coping—the use of denial defenses—have a negative influence on health outcomes, particularly in the long term (25). Vigilant strategies, be they problem-focused behavioral or cognitive tactics, have been shown to lead to more favorable long-term outcomes, including less psychiatric distress (25). Indeed, in previous analyses we found that use of a denial coping style tended to be associated with elevated psychiatric distress among the men in our group, but use of active, problem-focused coping was associated with relatively lower psychiatric distress levels (5). However, what appeared somewhat helpful for their husbands did not appear at all helpful for wives, especially those whose husbands were HIV seropositive: among these women, their husbands' use of active cognitive coping in the context of HIV infection was associated with elevated symptoms. In contrast, the husbands' use of avoidance coping in this domain was associated with reduced symptom levels among their wives. We believe that this reflects a more general coping pattern among these women, who, from their qualitative comments, often attempted to minimize the threat of HIV infection in their own and their husbands' lives. For example, one woman said, "The AIDS issue . . . is an aspect that is constantly in both my and [my husband's] mind, but we try to subdue it, not dwell on it, and lead as normal and healthy a life as possible." Another said, "When the AIDS scare hit, I felt it was a curse. Now I know that whatever happens is meant to be."

It is important to acknowledge several study limitations. First, our relatively small study group limited the power of the analyses. However, in cases where we found no significant differences (e.g., between psychiatric distress levels in women married to HIV-seropositive men versus those married to HIV-seronegative men), we also determined that effect sizes were small. Second, our small study group precluded examination of diagnosable psychiatric disorders as outcome variables. Replication with a larger study group in which other partner/caregiver relationships exist—e.g., that of nonspouse family member, lover, friend, or volunteer buddy—would be important next steps in examining the impact of psychosocial factors on diagnosable disorder among caregivers of HIV-seropositive persons. It would also be important to expand examination of these effects to other areas of the caregiver's life, such as use of health care services and general physical health. Finally, because the direction of causality cannot be firmly asserted with our cross-sectional data, replication using a stronger longitudinal design is critical to determine the generalizability and ultimate interpretation of our findings.

Despite these limitations, the present data remain important in that they examine the partners of HIV-seropositive individuals, a group virtually ignored in previous empirical research. Clearly, from a clinical perspective, the HIV status of one's partner may appear to be the most salient stressor in an individual's environment. However, other factors—namely, perceptions of personal risk of AIDS, experience of other life events, and the partner's use of particular coping styles—appear to be the principal correlates of psychiatric distress. These findings have clear implications for mental health interventions with the caregivers of HIV-infected individuals. The manner by which HIV infection acts as a stressor for these caregivers may be primarily indirect, mediated by other psychosocial characteristics of the caregivers as well as the infected individuals themselves.

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# Disturbances of Hypothalamic-Pituitary-Adrenal Axis Functioning During Ethanol Withdrawal in Six Men

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*Objective: Excessive exposure to glucocorticoids can have neurotoxic effects. The behavioral, cognitive, and neurochemical changes observed following the cessation of heavy drinking, therefore, may be associated with disturbances of the hypothalamic-pituitary-adrenal (HPA) axis. To investigate HPA axis disturbances during the ethanol withdrawal syndrome, the authors examined diurnal changes in plasma cortisol in six alcohol-dependent men following the abrupt discontinuation of alcohol intake. Method: Plasma cortisol concentrations were quantified every 30 minutes for 24 hours in the early stage (1 day after cessation) and the middle to late stage (3 days after cessation) of the ethanol withdrawal syndrome as well as after the resolution of acute symptoms (8 days or more after cessation). Results: Plasma cortisol concentrations were almost twice as high during acute withdrawal as they were following recovery. The duration of the cortisol diurnal cycle on the first day of withdrawal was negatively correlated with the severity of withdrawal. Conclusions: There is a marked activation of the HPA axis associated with the ethanol withdrawal syndrome. The authors hypothesize that this activation may account for some of the signs and symptoms of acute and subacute withdrawal. They discuss the potential long-term physiological effects of the episodic increases in cortisol associated with repeated episodes of ethanol withdrawal. The alterations in cortisol rhythmicity during early withdrawal may also have clinical implications.*

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The ethanol withdrawal syndrome is characterized by disturbances in the regulation of various neurophysiological processes (1), as manifested by noradrenergic hyperactivity, reduced γ-aminobutyric acid (GABA)-ergic functioning, and activation of the hypothalamic-pituitary-adrenal (HPA) axis. Alterations in these systems are associated with symptoms of ethanol withdrawal such as tremor, diaphoresis, depression, irritability, nausea and vomiting, tachycardia, and elevated blood pressure.

Elevations in glucocorticoid output have been associated with alterations in CNS physiology, biochemistry, and structure. Changes in this stress-response system during ethanol withdrawal may therefore contribute to both the acute and chronic changes noted in alcohol-dependent patients during abstinence. To investigate the pathophysiology of HPA axis disturbances during ethanol withdrawal, we examined diurnal changes in plasma cortisol in six alcohol-dependent men following the cessation of heavy drinking. Plasma cortisol concentrations were quantified every 30 minutes for 24 hours in the early stage and the middle to late stage of the ethanol withdrawal syndrome as well as after the resolution of acute symptoms. A preliminary report on this study was published in 1988 (2).

## METHOD

Six alcohol-dependent men (mean±SD age=39.7±10.2 years) were studied on the National Institute on Alcohol Abuse and Alcoholism research unit at the National Institutes of Health Clinical Center. Before admission to the study, they consumed a mean of more than 150 ml (mean±SD=266±87 ml) of absolute eth-

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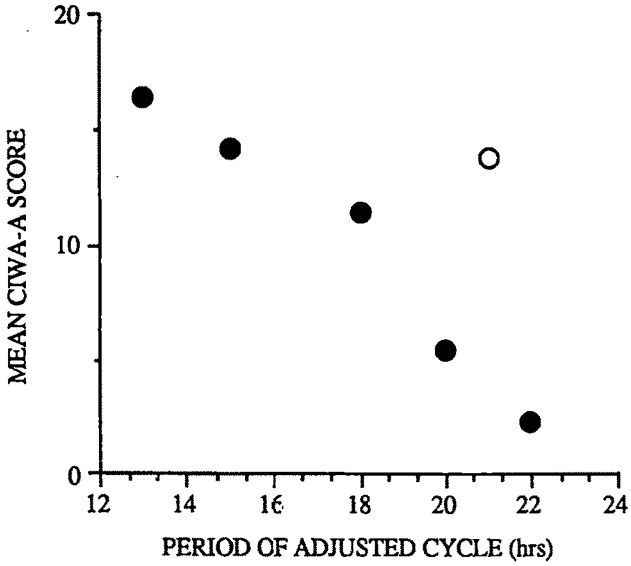
The authors thank Mr. Robert R. Rawlings for statistical advice and the inpatient nursing staff and research technicians of the National Institute on Alcohol Abuse and Alcoholism for their assistance.

**FIGURE 1. Correlation[a] of Period of Diurnal Cortisol Cycle With Severity of Ethanol Withdrawal[b] on Day 1 of Withdrawal for Five Alcohol-Dependent Subjects**



[a] $r=-0.98$, $df=4$, $p<0.005$. The cycle period was adjusted for the best-fit duration. One patient (open circle) was not included in the analysis because he had ingested a benzodiazepine 1 day before the study.

[b] Mean score on the Clinical Instrument for Withdrawal Assessment—Alcohol (CIWA-A).

anol daily. They all claimed that their last drink was within 24 hours of admission.

On admission, the mean breath alcohol concentration of the six men was 110±30 mg/100 ml. All were drug free on admission (verified by urine drug screen) except one patient, who later acknowledged taking 0.25 mg of alprazolam the day before admission. (The data for this patient were excluded from analysis.) These patients met *DSM-III* criteria for alcohol dependence, had Michigan Alcohol Screening Test (3) scores indicative of alcoholism (35.7±10.4; range=19–48), and met Research Diagnostic Criteria (4) for alcoholism. Six male control subjects (42±16.6 years old) ($t=0.4$, $df=11$, n.s.) were also evaluated. They were free of past or present *DSM-III* axis I or II diagnosis. Written informed consent was obtained from all subjects. The alcohol-dependent patients were admitted to the inpatient unit at approximately 9:00 a.m. Study days (5:00 p.m. through 5:00 p.m.) were as follows: day 1=day of admission, day 3=24 hours following completion of day 1 (obtained for five patients); day 8+ =at least 1 week following admission (four patients on day 8, one on day 23, and one on day 30). Breath alcohol concentrations were less than 50 mg/100 ml (mean=20±10 mg/100 ml) when the study was initiated. Control subjects were hospitalized for one night before the study and for another night while cortisol concentrations were obtained; cortisol concentrations were obtained from 3:00 p.m. through 3:00 p.m. Plasma cortisol was determined by using radioimmunoassay (5). The samples were obtained every 30 minutes in alcohol-dependent subjects and every hour in control subjects. Severity of ethanol withdrawal was quantified by using a validated rating scale (the Clinical Instrument for Withdrawal Assessment—Alcohol) (6). These ratings were determined hourly (while awake) on day 1 and every third hour on day 3 and day 8+. Plasma cortisol concentrations and Clinical Instrument for Withdrawal Assessment—Alcohol scores are presented as the means plus or minus the standard deviations of all values in a 24-hour period.

## RESULTS

The mean plasma cortisol concentrations on day 1 and day 8+ of withdrawal of five patients were compared by using paired t test. Since no data were available for one of these patients on day 3, this day was excluded from analysis; the data from the patient who gave himself a benzodiazepine before admission was also not included in the analysis. The highest mean plasma cortisol concentrations on the first day of withdrawal (15.3±4.3 μg/dl) coincided with peak withdrawal symptoms (mean Clinical Instrument for Withdrawal Assessment—Alcohol score=10.6±2.2). Day 1 cortisol concentrations were significantly higher than those following recovery on day 8+ (9.0±2.0 μg/dl) ($t=3.05$, $df=4$, $p<0.05$) (mean Clinical Instrument for Withdrawal Assessment—Alcohol score on day 8+=1.4±0.6). The day 3 mean cortisol concentrations ($N=4$, 11.9±3.8 μg/dl) were between the day 1 and day 8+ levels. Significant differences in mean cortisol concentrations were observed between control subjects (10.3±1.0 μg/dl) and patients on day 1 ($t=3.19$, $df=9$, $p<0.02$); there were no differences between control subjects and patients on day 8+ ($t=1.39$, $df=9$, n.s.).

To examine the relationship of plasma cortisol diurnal rhythmicity and severity of the ethanol withdrawal syndrome, we used cosine analysis to characterize potential variations in diurnal cortisol secretion cycle length. On day 1 of withdrawal, three of the five patients exhibited a cycle length shorter than that of any of our control subjects (range=20–22 hours). A strong negative correlation was evident between the duration of the adjusted cycle length on day 1 and the severity of withdrawal (figure 1). The patient who gave himself a benzodiazepine before admission, excluded from the preceding analysis, demonstrated an adjusted cycle length on day 1 similar to that of the control subjects, despite moderate withdrawal symptoms (his mean Clinical Instrument for Withdrawal Assessment—Alcohol score=14.5) and marked hypercortisolemia (mean cortisol level=15.4 μg/dl) (figure 1).

## DISCUSSION

This study has several methodological shortcomings, including small size, different periods of acclimation to the environment, a limited sampling period to evaluate diurnal rhythmicity, and differences in the timing of day 8+. Despite these limitations, there were consistent findings of a sustained elevation of plasma cortisol concentrations in five alcohol-dependent patients during the ethanol withdrawal syndrome.

Both the glucocorticoids and chronic alcohol use influence a diverse array of physiological processes (7), such as immune function, sleep, glucose metabolism, cardiovascular function, prostaglandin synthesis, and catecholamine and serotonin functions. Since many alcohol-dependent individuals experience repeated episodes of ethanol withdrawal, the associated episodic increases in cortisol may be responsible in part for the changes noted in these processes following chronic alcohol use. For example, the putative neurotoxic effects of increased corticosteroid concentrations (8), perhaps in combination with the direct toxic effects of alcohol, thiamine deficiency, and/or sleep apnea, may contribute to the cognitive impairments associated with chronic alcohol dependence. In addition, the elevated levels of cortisol associated with the cessation of ethanol intake in the alcohol-dependent patient may account for some of the signs and symptoms of acute and subacute withdrawal, such as fatigue, weakness, depression, elevated blood pressure, and confusion.

Current recommendations for the treatment of uncomplicated ethanol withdrawal suggest the selective use of pharmacotherapy; it is generally considered acceptable to treat mild withdrawal with supportive therapy only (1). If toxic effects of withdrawal-associated hypercortisolemia can be conclusively demonstrated, more aggressive pharmacotherapy may be suggested in the future.

The alterations in cortisol rhythmicity during early withdrawal may also have clinical implications. This change may be specific to the HPA axis or may be evidence of more widespread systemic desynchronization of the "biological clock," perhaps due to an alcohol-induced or withdrawal-induced defect in the suprachiasmatic nucleus. Alterations in physiological rhythms have been associated with disturbances in mood and sleep, both of which are commonly observed during chronic alcohol intake and the withdrawal syndrome. The one patient who took alprazolam the day before admission demonstrated a normal diurnal plasma cortisol rhythm despite high cortisol levels. Since benzodiazepines have been shown to "entrain" the desynchronization of circadian rhythms (9), alprazolam may have normalized this patient's circadian rhythmicity without attenuating HPA axis activation.

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# Childhood Antecedents of Homelessness in Psychiatric Patients

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*Objective: This study examined the relationship between childhood experience and homelessness in psychiatric patients. Method: Three large and diverse samples of homeless patients (N=512) were compared with a sample of patients who had never been homeless (N=271), with respect to childhood experience of foster care, group home placement, and running away. One of the homeless samples and the never homeless sample were drawn from patients admitted to a state mental hospital. In this state hospital population, risk ratios for lifetime prevalence of homelessness could be derived. Results: In the three homeless samples, over 15% had a history of foster care, over 10% had a history of group home placement, and over 20% had a history of running away. These figures compared with 2%, 1%, and 5%, respectively, in the never homeless sample. In the state hospital, the lifetime prevalence of homelessness in patients with any one of these childhood experiences was about threefold that of other patients. A history of homelessness was reported by the great majority of state hospital patients who had had one of these childhood experiences. Conclusions: These childhood experiences were strongly associated with adult homelessness in these psychiatric patients. It might be possible to prevent homelessness in some cases by interventions aimed at patients with such childhood histories.*

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This paper reports on the relationship between childhood experiences and homelessness in psychiatric patients. Recent studies (1–3) affirm that in the United States, homelessness has had an especial impact on psychiatric patients. Yet empirical data on which psychiatric patients are at highest risk for homelessness are limited (4, 5).

We examine potential childhood antecedents of homelessness, namely, placement in foster care, placement in a group home, and running away for 1 week or longer. Three studies, taken together, test for associations among these childhood experiences and adult homelessness in psychiatric patients. In short, we compare three large and diverse samples of homeless patients with a never homeless reference group, with respect to these childhood experiences.

In the first study, in former psychiatric inpatients in New York City municipal shelters, we found a high frequency of these childhood experiences (6). In the second study, we replicated this finding in nonshelter homeless patients admitted to an urban psychiatric hospital by street outreach teams. In the third study, we tested the findings of the first two studies in a population of patients admitted to a suburban state mental hospital. This population provided a never homeless reference group as well as a third group of homeless patients. In addition, the third population allowed us to obtain risk ratios for the factors under study.

A childhood experience that predicts adult homelessness may not itself be a cause of homelessness, but rather may serve as a marker for associated processes in the individual, in the family, or in their interrelationship that are causally related to homelessness in adulthood. Nonetheless, the establishment of an association between a childhood experience and subsequent homelessness can be a significant step in elucidating the causes of homelessness. Further, the

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identification of a subgroup of patients at high risk for homelessness can have implications for intervention.

## METHOD

### *Subjects*

*Shelter sample.* In 1985 we interviewed a sample of men and women staying in the New York City municipal shelter system (N=1,092) (7), as well as a separate sample of new arrivals at the men's shelters (N=223) (2). The sampling strategies (aimed at representative samples) and the findings have been reported elsewhere (2, 7). Here we consider only the 81 women and the 165 men (33 men were from the sample of new arrivals) with a history of admission to a psychiatric hospital, henceforth referred to as the shelter patients.

*Bellevue sample.* In 1987 the mayor of New York City broadened the interpretation of involuntary commitment laws. Homeless mentally ill persons outside of municipal shelters who were unable to care for themselves were to be admitted to Bellevue Hospital (8). Most were identified by outreach teams in midtown Manhattan. Ward staff were asked to complete questionnaires for the 174 patients admitted over the initial 6 months of the program. Seven subjects refused to participate, and information was incomplete for seven others.

*State hospital sample.* In 1988–1989 we collected data on patients admitted to Rockland Psychiatric Center, a New York state mental hospital that provides long-term inpatient care for patients in two suburban counties and for some from New York City. At the time of the study, the hospital also admitted patients directly from emergency rooms.

The state hospital sample comprises 377 admitted patients. Of 556 patients admitted for at least 1 week between September 1988 and April 1989, 440 were assigned to social workers, who returned a questionnaire on every patient assigned to them; information was complete on 377 (86%) of these. The remaining 116 patients were assigned to three social workers, who returned questionnaires on only 57 of them. To avoid possible bias in the selection of these 57 patients from the 116, we excluded the entire 116. Since patients were assigned to social workers in systematic rotation, bias due to the exclusion of the entire 116 was unlikely.

### *Procedure*

*Shelter sample.* The interview included structured questions on out-of-home placements (including foster care and group home placements) and behavioral problems (including running away) in childhood (2, 7).

*Bellevue sample.* The questionnaire included the questions on foster care and group home placement used in the shelter study but not questions on running away. Questionnaires were completed by ward staff (generally a social worker or community liaison worker), who used information from any available sources (patient, relatives, outreach team, charts).

*State hospital sample.* Social workers were trained and supervised in the use of a questionnaire in the course of the psychosocial assessment. It included the same questions on childhood experiences as were used in the shelter and the Bellevue samples. The section on homelessness elicited the cumulative time spent homeless in three overlapping time periods: the past 3 months, the past 3 years, and since age 17. Homelessness was defined as sleeping in shelters or public places from age 17 onward. Structured questions and guidelines were provided for interviewers.

The reliability of the responses on homelessness was checked in 17 patients who remained on the admission wards after the end of the study and were reinterviewed in a blind manner by a social worker. For the dichotomy ever homeless/never homeless in adult lifetime, the focus of this paper, there was complete agreement. Both interviewers rated the same seven patients as ever homeless.

Diagnoses were obtained from the computerized information system used by New York state hospitals. Patients with a drug- or alcohol-related diagnosis (primary or nonprimary) in the present or a previous admission were considered to have a history of drug or alcohol abuse.

### *Data Analysis*

The three homeless samples were each compared with the never homeless state hospital patients with respect to the proportion of patients who had had each childhood experience. Odds ratios were not used because with a common outcome (such as homelessness in psychiatric patients), they do not give good estimates of relative risks.

In analyses restricted to the state hospital population, lifetime prevalence ratios were obtained. Lifetime prevalence ratios were defined as the proportion ever homeless in patients with the childhood experience divided by the proportion ever homeless in patients without the childhood experience. Logistic regression was used in multivariate analyses in this population, since the dependent variable was the binary outcome ever/never homeless (9). Adjustment was made for several potential confounding or intervening variables. Because of the overlap between childhood experiences and the small numbers of patients reporting them, each childhood variable was tested individually for significance as a predictor of homelessness without controlling for the other childhood variables. Odds ratios based on logistic regression are not reported (see earlier discussion).

**TABLE 1. Prevalence of Childhood[a] Foster Care, Group Home Placement, and Running Away Among Homeless and Never Homeless Psychiatric Patients**

| Sample and Childhood Experience | Total | | Male | | Female | | Age (years) | | | | Ethnic Group | | | | Catchment Area[b] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | <40 | | ≥40 | | Black | | Other | | New York City | | Other | |
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| Never homeless patients in state hospital | 271 | 100 | 169 | 100 | 102 | 100 | 194 | 100 | 77 | 100 | 137 | 100 | 134 | 100 | 124 | 100 | 147 | 100 |
| Foster care | 5 | 2 | 3 | 2 | 2 | 2 | 4 | 2 | 1 | 1 | 5 | 4 | 0 | 0 | 2 | 2 | 3 | 2 |
| Group home | 4 | 1 | 1 | 1 | 3 | 3 | 3 | 2 | 1 | 1 | 4 | 3 | 0 | 0 | 1 | 1 | 3 | 2 |
| Runaway | 14 | 5 | 9 | 5 | 5 | 5 | 13 | 7 | 1 | 1 | 9 | 7 | 5 | 4 | 4 | 3 | 10 | 7 |
| Ever homeless | | | | | | | | | | | | | | | | | | |
| State hospital patients | 106 | 100 | 70 | 100 | 36 | 100 | 83 | 100 | 23 | 100 | 57 | 100 | 49 | 100 | 62 | 100 | 44 | 100 |
| Foster care | 19 | 18 | 13 | 19 | 6 | 17 | 16 | 19 | 3 | 13 | 13 | 23 | 6 | 12 | 8 | 13 | 11 | 25 |
| Group home | 16 | 15 | 14 | 20 | 2 | 6 | 13 | 16 | 3 | 13 | 10 | 18 | 6 | 12 | 7 | 11 | 9 | 20 |
| Runaway | 26 | 25 | 20 | 29 | 6 | 17 | 22 | 27 | 4 | 17 | 19 | 33 | 7 | 14 | 18 | 29 | 8 | 18 |
| Bellevue patients | 160 | 100 | 101 | 100 | 59 | 100 | 71 | 100 | 89 | 100 | 62 | 100 | 98 | 100 | — | — | — | — |
| Foster care | 27 | 17 | 17 | 17 | 10 | 17 | 12 | 17 | 15 | 17 | 14 | 23 | 13 | 13 | — | — | — | — |
| Group home | 17 | 11 | 14 | 14 | 3 | 5 | 8 | 11 | 9 | 10 | 9 | 15 | 8 | 8 | — | — | — | — |
| Runaway[c] | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| Shelter patients | 246 | 100 | 165 | 100 | 81 | 100 | 176 | 100 | 70 | 100 | 165 | 100 | 81 | 100 | — | — | — | — |
| Foster care | 54 | 22 | 38 | 23 | 16 | 20 | 38 | 22 | 16 | 23 | 44 | 27 | 10 | 12 | — | — | — | — |
| Group home | 44 | 18 | 31 | 19 | 13 | 16 | 36 | 20 | 8 | 11 | 33 | 20 | 11 | 14 | — | — | — | — |
| Runaway | 48 | 20 | 37 | 22 | 11 | 14 | 33 | 19 | 15 | 21 | 30 | 18 | 18 | 22 | — | — | — | — |

[a] Before age 17.

[b] Bellevue and shelter samples were from New York City.

[c] Questions on running away were not asked in Bellevue sample.

## RESULTS

Foster care was reported by more than 15% of the patients in each of the three homeless samples and by 2% of the never homeless state hospital patients (table 1). Group home placement was reported by more than 10% of each of the three homeless samples and by 1% of the never homeless. Running away was reported by 20% or more of each of two homeless samples and by 5% of the never homeless. Within all major demographic subgroups these three childhood experiences were consistently more common in the three homeless samples than in the never homeless (table 1). This also held true within diagnostic subgroups (data available from Dr. Susser).

Homelessness at some time since age 17 was reported by 79% of the state hospital patients who had received foster care, 80% of those who had been in group homes, 65% of those who had been runaways, and 21% of those who had had none of these childhood experiences. Lifetime prevalence ratios are presented in table 2.

Many state hospital patients reported more than one of these childhood experiences. Patients with a history of group home placement were especially likely to report one of the other childhood experiences; in 20 such patients, 16 had a history of foster care or of running away.

**TABLE 2. Relationship Between Homelessness and Childhood Foster Care, Group Home Placement, and Running Away in 377 Patients in a State Mental Hospital**

| Group | N | Ever Homeless | | Lifetime Prevalence Ratio | 95% Confidence Interval |
|---|---|---|---|---|---|
| | | N | % | | |
| Foster care | | | | 3.2 | 2.4, 4.2 |
| Yes | 24 | 19 | 79 | | |
| No | 353 | 87 | 25 | | |
| Group home[a] | | | | 3.2 | 2.4, 4.2 |
| Yes | 20 | 16 | 80 | | |
| No | 356 | 89 | 25 | | |
| Runaway[b] | | | | 2.7 | 2.0, 3.7 |
| Yes | 40 | 26 | 65 | | |
| No | 334 | 79 | 24 | | |

[a] Data missing for one patient.

[b] Data missing for three patients.

In a logistic regression, adjustment was made for the following variables: age group (younger than 40, 40 or older), ethnicity (black, other), gender, catchment area (New York City, other), diagnosis (schizophrenia related, other), drug abuse history (present, absent), and alcohol abuse history (present, absent). Histories of foster care ($p<0.0001$), group home placement ($p<0.0001$), and running away ($p<0.0001$) were each highly significant.

The utility of these logistic regression models in the prediction of homelessness was examined. In terms of sensitivity, with only the control variables (given earlier) in the model, none of the ever homeless had an estimated probability of homelessness greater than 0.50; however, when one of the childhood variables was added to the model, 19%, 15%, and 24% of the ever homeless had a probability of homelessness greater than 0.50 for foster care, group home placement, and running away, respectively. In terms of specificity, with only the control variables in the model, 99% of the never homeless had a probability of homelessness less than 0.50; when the childhood variables were added, 97%, 98%, and 97% of the never homeless had a probability of homelessness less than 0.50 for foster care, group home placement, and running away, respectively. Further, the sample was then split randomly into two subsamples, one for fitting these models and the other for testing the predictive power; the sensitivities and specificities remained essentially the same.

## DISCUSSION

A history of foster care, group home placement, or running away for 1 week or longer was common in the three large and diverse samples of homeless inpatients and not in the sample of never homeless inpatients. In state mental hospital patients, the lifetime prevalence of homelessness in patients with a history of foster care, group home placement, or running away was found to be approximately threefold that of other patients. In a logistic regression each of these variables remained highly significant ($p<0.0001$) after potential confounding and intervening variables were controlled. In fact, the great majority of state hospital patients with these childhood histories had been homeless at some time—79% of those with a history of foster care, 85% of those with a history of group home placement, and 65% of those with a history of running away. These figures may yet underestimate their lifetime risk of homelessness, since the patients had not completed their life course.

### *Caveats*

First, homelessness far in the past may have been underreported by state hospital patients. Second, 26 of the 106 ever homeless state hospital patients had a relatively short experience of homelessness of less than 1 month. Third, some of the potential sample in the state hospital was lost because three less diligent social workers returned questionnaires on only 57 of the 116 patients assigned to them. Fourth, for some purposes current (rather than lifetime) homelessness is more instructive.

We examined the potential effect of these factors on the results by repeating the logistic regression analyses under the following circumstances: 1) using only patients who were judged by social workers to be good informants (to minimize bias due to underreporting); 2) using homelessness of more than 1 month as the dependent variable (to exclude short episodes of homelessness); 3) with the inclusion of the 57 questionnaires that were returned by less diligent social workers (to check for bias in sampling); and 4) with ever/never homeless in the past 3 months as the dependent variable (to examine the effect of childhood experience on current homelessness). In every case, a history of foster care, group home placement, and running away remained highly significant.

Two other potentially relevant childhood experiences were tested in the logistic regression analysis (not shown in results). Being sent to jail or reform school was not a significant predictor of homelessness ($p=0.48$). Placement in a special residence for children with disabilities was significant at the 0.05 level ($p=0.02$), but its association with homelessness was much weaker than that of foster care, group home placement, and running away.

### *Implications for Intervention*

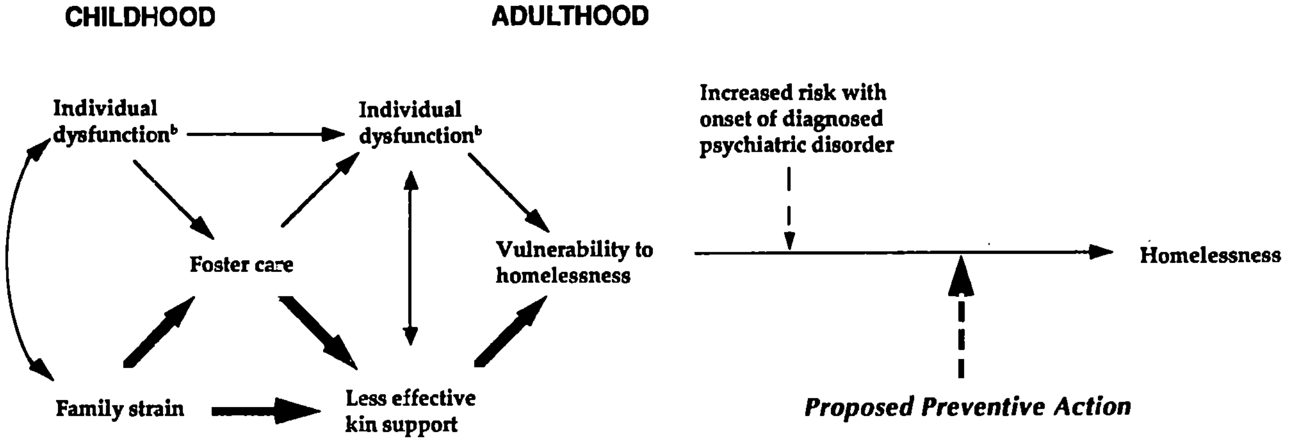
A program aimed at patients with these childhood histories might prevent homelessness in some cases. Foster care, group home placement, and running away have several salient attributes that would be conducive to the success of a preventive intervention. These childhood experiences precede homelessness, are stable characteristics, are easily assessed, strongly predict homelessness, and mark a group at extremely high risk for homelessness. They also relate to a substantial portion of the risk of homelessness, either directly or as markers for other factors; the attributable risk (or etiologic fraction) (10) for homelessness due to any one of the three was 25%. Thus, an effective intervention could have a significant impact on the occurrence of homelessness in psychiatric patients.

Elucidation of the causal processes that underlie the association among these childhood experiences and adult homelessness in psychiatric inpatients will surely advance the possibility of effective intervention. As noted earlier, even though a childhood experience strongly predicts adult homelessness, it may not itself be a cause of homelessness. For instance, family and individual problems associated with foster care in childhood (e.g., poverty, death of a mother, abuse, or neglect) may be causally related to adult homelessness, while the experience of foster care itself may have little or no effect. Yet in this case foster care, as a marker, will be a predictor of homelessness.

Some of the causal pathways that might link foster care in childhood to adult homelessness are depicted in figure 1. On the basis of available theory (11–14) and data (15–18), it is hypothesized that the vulnerability of former foster children to homelessness is due largely to their less effective kin support (figure 1). In the case of group home placement and running away, however, individual dysfunction (e.g., drug abuse) would be expected to play a more prominent role (19–21).

Efforts to reduce homelessness in these high-risk patients need not and should not be postponed until such knowledge is available. A straightforward approach would involve identifying patients with these childhood histories at the time of their first admission to a psychiatric hospital, with a simple set of screening questions. Such patients would be offered ongoing access to a service designed to assist patients in tasks directly related to housing, such as locating emergency

**FIGURE 1. A Causal Model of Childhood Foster Care and Adult Homelessness in Psychiatric Patients**[a]


CHILDHOOD
ADULTHOOD
Individual dysfunction[b]
Individual dysfunction[b]
Foster care
Vulnerability to homelessness
Family strain
Less effective kin support
Increased risk with onset of diagnosed psychiatric disorder
Homelessness
Proposed Preventive Action

[a] Thicker lines indicate that family strain is hypothesized to have a greater effect than individual dysfunction.

[b] In the child, refers to emotional and behavioral problems, as well as physical disabilities, and may include premorbid signs of psychiatric disorders diagnosed in adulthood. In adulthood, also included are problems in social adaptation, e.g., illiteracy, substance use, premarital pregnancy, and less resilience to adverse events without otherwise overt dysfunction.

and long-term accommodations and setting aside money to pay the rent.

Finally, we underscore that homelessness is a trauma affecting large numbers of psychiatric patients in the United States. Further research on the causes of homelessness and preventive interventions for high-risk subgroups may help to alleviate the problem. These efforts should be accompanied by attempts to achieve the fundamental changes in housing and mental health policies required to prevent homelessness in all mental patients (22).

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# Screening for Dysfunction in the Children of Outpatients at a Psychopharmacology Clinic

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*Objective: The goals of this study were 1) to determine whether the use of the Pediatric Symptom Checklist in an adult-oriented psychiatric practice was feasible, 2) to determine if scores indicative of dysfunction on the Pediatric Symptom Checklist were associated with parental or background factors, 3) to determine whether children flagged by their scores on the Pediatric Symptom Checklist were receiving psychiatric services, and 4) to compare the psychosocial dysfunction in this group of children with that found in children screened as part of routine pediatric visits. Method: Adult outpatients in a hospital's clinical psychopharmacology unit were asked to complete the Pediatric Symptom Checklist regarding their children. These patients were the parents of 100 school-aged children. Factors such as the parents' diagnoses and demographic variables were also examined. Results: The Pediatric Symptom Checklist was readily accepted by parents and fit easily into the routine of general psychiatric practice. Significantly more of the children of these outpatients than of children in comparable pediatric offices had scores indicative of psychiatric dysfunction (scores above the cutoff). Children of parents who were single, of low socioeconomic status, or with a diagnosis of personality (especially borderline) or mood disorder were more likely to have scores above the cutoff. More than a third of the children who had scores above the cutoff on the Pediatric Symptom Checklist were not currently receiving psychiatric services. Conclusions: The Pediatric Symptom Checklist provided a rapid and simple method for general psychiatrists to identify psychosocial dysfunction in their patients' children.*

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Research indicates that children of psychiatric patients are at high risk for psychiatric disorders and dysfunction. The risks stem from genetic factors, the impact of being raised by an emotionally disordered parent, and the high rate of secondary stressors such as divorce and parental hospitalization (1). However, as highlighted by Philips (2), clinicians who treat adults often overlook the facts that their patients may be parents and that their children may require psychiatric attention.

Early studies (3) as well as more recent work (4–6) demonstrate that children of mothers with schizophrenia are at much higher risk for both schizophrenic disorders and other psychiatric disorders. Investigators have also documented the high risk among children of parents with affective disorders (7–11). Weissman et al. (12) found a high rate of major depression (37%), a serious risk of substance abuse, and poorer overall functioning in 220 children of depressed parents.

The children of parents with anxiety disorders are also at risk. Turner et al. (13) found that children of parents with anxiety disorders were more anxious and fearful, reported more school difficulties and somatic complaints, and were more likely to have psychiatric disorders than comparison groups of children whose parents did not have anxiety disorders. Rosenbaum et al. (14) determined that "behavioral inhibition to the unfamiliar" was highly prevalent in children whose parents had panic disorder and agoraphobia. They concluded that these children were at risk for later psychiatric disorder.

Less attention has been focused on children of parents with personality disorders. However, in an investigation of 137 psychiatric patients with various diagnoses, Rutter and Quinton (15) reported that children of parents with personality disorders were at even greater risk than children of parents with psychotic or affective disorders.

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Other studies have examined the children of psychiatric outpatients with a full range of diagnoses. Orvaschel et al. (16) determined that 43% of 28 children of parents with psychiatric disorders had psychiatric disorders themselves, and Feldman et al. (17) found that 39% of 306 children of parents with psychiatric disorders had received psychiatric diagnoses.

Despite the consensus regarding the high rate of psychopathology and dysfunction in the children of psychiatric patients, investigators have reported that many of these children are not identified and do not receive needed services. Orvaschel et al. (16), for example, found that 42% of the children diagnosed with a psychiatric disorder in their study had never received any treatment. Several recent reports (18–20), including one by the Institute of Medicine (20), have highlighted the need for primary and secondary prevention efforts with the children of psychiatric patients.

One approach to increasing services for children at risk for psychopathology and dysfunction is to step up efforts to identify those most in need by instituting systematic screening procedures. To be successful, screening procedures must fit into the pattern of clinical practice; therefore, they must be brief and simple (21).

In pediatric settings, parental reports, especially symptom checklists, have been found to be a useful method of screening children's psychosocial functioning (22; unpublished 1989 paper by J.M. Murphy et al.); however, similar screening methods for the children of psychiatric patients have not been investigated. Since screening relies on parental reporting, the most obvious question is whether parents who are psychiatrically ill can provide reliable and valid reports. Although it is clear that parental reports of child behavior can be influenced by a variety of factors, including the parent's own adjustment (23, 24), there is also evidence to suggest that even psychiatrically ill parents can be accurate reporters. For example, investigations comparing reports of such parents with reports from clinicians, teachers, and the children themselves (10, 17) found no major inconsistencies associated with parental psychiatric disorder. Given the practical need for and limitations of screening using brief questionnaires, extensive research with specific groups will be necessary to know the nature and meaning of parental reporting.

## THE PEDIATRIC SYMPTOM CHECKLIST

The screening instrument chosen for the current study was the Pediatric Symptom Checklist (25) (appendix 1). The Pediatric Symptom Checklist is a 35-item questionnaire that takes less than 5 minutes to complete and score. The answers reflect the parent's view of his or her school-aged child's psychosocial functioning. Using an empirically defined cutoff point (26), the Pediatric Symptom Checklist identifies dysfunctional children who are likely to benefit from further psychiatric evaluation.

The validity and reliability of the Pediatric Symptom Checklist have been demonstrated in a variety of pediatric settings. Pediatric Symptom Checklist scores have been compared with child assessments based on in-depth interviews, other validated questionnaires, and data from children's daily lives. In a study conducted in two middle-class pediatric practices (27), results indicated 79% agreement (kappa=0.60) between Pediatric Symptom Checklist scores and clinicians' ratings of psychosocial dysfunction, with a sensitivity of 0.95 and a specificity of 0.68. In the same study, the overall agreement between the Pediatric Symptom Checklist and presence of a serious psychiatric diagnosis was 87% (kappa= 0.74, sensitivity=0.87, specificity=0.89). Test-retest reliability between two administrations of the Pediatric Symptom Checklist about 4 weeks apart was r=0.86. These findings were replicated independently by other investigators using a different group of children on a military base (28).

Acceptable levels of reliability as well as high levels of overall agreement between Pediatric Symptom Checklist scores and clinicians' ratings of psychosocial dysfunction have also been found with economically disadvantaged and minority group children (29) and in a study conducted in an inner-city pediatric clinic (unpublished 1989 paper by J.M. Murphy et al.). These results suggest that the Pediatric Symptom Checklist is valid and reliable for screening children from disadvantaged and minority backgrounds as well as for children in middle-class settings. Another investigation (26) found high levels of overall agreement (89%, kappa=0.52) between the Pediatric Symptom Checklist and the Child Behavior Checklist, along with acceptable levels of test-retest reliability (r=0.86).

In terms of daily functioning, 87% of a group of children referred to a clinic for psychiatric evaluation had scores above the cutoff on the Pediatric Symptom Checklist (26). Investigators in a public middle school setting (30) reported an 83% agreement between Pediatric Symptom Checklist scores and counselors' assessments of student functioning as well as an 84% level of agreement between parents' reports on the Pediatric Symptom Checklist and children's self-reported Pediatric Symptom Checklist scores. These authors also found that 42% of the children who had scores above the cutoff later failed a course, compared with 20% of the children with scores below the cutoff. The results of this study demonstrated the validity of the Pediatric Symptom Checklist by using the objective outcome criterion of school performance independent of parental reports.

The present study is to our knowledge the first to use the Pediatric Symptom Checklist as a brief screening procedure for the children of psychiatric outpatients. The goals of the study were 1) to determine whether the use of the Pediatric Symptom Checklist in an adult-oriented psychiatric practice was feasible, 2) to determine if scores above the cutoff on the Pediatric Symptom Checklist were associated with any particular parental or background factors, 3) to determine whether children flagged by their scores on the Pediatric Symptom Checklist were receiving psychiatric services, and 4) to compare the rate of psychosocial dysfunction in this group of children with that found in children screened as part of routine pediatric visits.

## METHOD

The study was conducted in a hospital clinical psychopharmacology unit, an outpatient clinic emphasizing psychotropic treatment of anxiety and affective disorders and related clinical research. All English-speaking patients who had children 6–12 years old and who had scheduled appointments during the study period were considered eligible. A research assistant approached eligible patients in the waiting room and asked them to fill out a Pediatric Symptom Checklist for each of their children. Participation was completely voluntary. After patients had completed the Pediatric Symptom Checklist, the research assistant told them about the interview phase of the study, asked whether they would agree to be potential subjects, and obtained written consent. We continued to recruit subjects until 100 completed Pediatric Symptom Checklists were obtained.

One hundred nine English-speaking patients with children in the target age range kept their appointments during the study period. We were able to approach 89 (82%) of these patients, and 80 (90%) of them agreed to participate. Seventy-four (93%) of the consenting patients completed the Pediatric Symptom Checklist. (Six patients who consented brought the Pediatric Symptom Checklist home to complete it but did not return it despite repeated in-person and telephone reminders. These patients had diagnoses similar to those of patients who completed the Pediatric Symptom Checklist.)

The 74 patients were from different families (no checklists were completed by spouses) and had 100 children 6–12 years old; 23 families had more than one child. In 18 of these families the siblings had concordant Pediatric Symptom Checklist results, and in five the siblings had discordant results (one or more of the children had scores above the cutoff and the remaining child or children had scores below the cutoff). The 21 children with Pediatric Symptom Checklist scores above the cutoff came from 17 different families (two families had two children with scores above the cutoff and one family had three children with scores above the cutoff). Sixty-two of the 100 children were boys, and 90 were nonminority. Their mean±SD age was 9.8±1.9 years. For 78 of the children, the patient was the mother. The parents' mean occupational status rating on the 9-point Hollingshead scale (29) was 5.4±2.4.

The Pediatric Symptom Checklist consists of 35 symptoms that parents rate as occurring "often," "sometimes," or "never" in the child. The Pediatric Symptom Checklist is scored by assigning 2, 1, or 0 points, respectively, to these ratings. An overall score is calculated by adding the points. For 6–12-year-old children, scores below the cutoff (27 and lower) are considered within the normal range. Scores above the cutoff (28 or higher) suggest dysfunction and the need for further evaluation. The Pediatric Symptom Checklist also requests data on the child's age, sex, and race as well as the parent's marital status and occupation. We coded occupational data and estimated family socioeconomic status by using the Hollingshead scale (31).

We obtained information regarding parents' diagnoses from their charts or from their psychiatrists. Diagnoses were made by experienced staff psychiatrists, all of whom routinely participate in clinical research protocols, and in accordance with *DSM-III-R*. We then grouped the diagnoses into broader categories (mood disorders, anxiety disorders, both, and other) according to *DSM-III-R*.

The study design called for interviews with the parents of all children with Pediatric Symptom Checklist scores of 28 or higher as well as a randomly selected equal number of parents whose children had scores lower than 28.

The research assistant, blind to the child's Pediatric Symptom Checklist score, conducted a semistructured telephone interview with the parent who had filled out the Pediatric Symptom Checklist. The purpose of the interview was to determine if children with Pediatric Symptom Checklist scores above the cutoff had been identified previously as having psychiatric difficulties and were receiving treatment.

We used chi-square tests to compare the rate of dysfunction in our study group of children, as screened by the Pediatric Symptom Checklist, with that found in pediatric study groups and to identify categorical factors which were significantly associated with higher levels of dysfunction.

The data for all 100 children were first analyzed; then data for only one randomly selected child from each family (N=74) were examined. Since the results were virtually identical, we report findings based on all 100 children.

## RESULTS

### *Pediatric Symptom Checklist*

Twenty-one of the children had Pediatric Symptom Checklist scores of 28 or higher: 13 (21%) of the 62 boys and eight (21%) of the 38 girls. In two other studies (26, 27), we found Pediatric Symptom Checklist scores above the cutoff in 12% and 11% of predominantly white, middle-class pediatric study groups. We used analysis of variance to compare the mean occupational status ratings found in these two studies—5.4 and 5.5—with that of our psychopharmacology clinic patients—5.4—and found no statistically significant difference (F=0.1, df=2, 569). When we combined the children from the two pediatric study groups (N=351), we found that 41 (12%) had Pediatric Symptom Checklist scores above the cutoff. The rate of 21% in the psychopharmacology clinic group was significantly higher ($\chi^2$=4.9, df=1, p<0.05).

In terms of axis I diagnoses, 50 children in the current study had a parent with an anxiety disorder (26 parents had panic disorder with agoraphobia, 16 had panic disorder without agoraphobia, five had generalized anxiety disorder, two had obsessive-compulsive disorder, and one had posttraumatic stress disorder). Twenty-eight had parents with a mood disorder (18 had major depressive disorder, six had bipolar disorder, and four had dysthymia/cyclothymia), and 16 had parents with both anxiety and mood disorders. Six children had parents with neither mood nor anxiety disorders; their diagnoses included attention deficit-hyperactivity disorder (four parents), adjustment disorder (one parent), and psychotic disorder (one parent).

Although the rate of children with Pediatric Symptom Checklist scores above the cutoff was about twice as high for children of parents with mood disorders (29%—eight of 28 children) as for those whose parents had anxiety disorders (16%—eight of 50 children), the differences by axis I diagnostic category did not reach statistical significance.

Seventeen children had parents with an axis II diagnosis. Seven (41%) of these 17 children had Pediatric Symptom Checklist scores above the cutoff, compared with 14 (17%) of the 83 children whose parents did not have an axis II diagnosis ($\chi^2$=3.7, df=1, p<0.06). Most of this difference appeared to be due to the particularly higher rate of scores above the cutoff in children of parents with the diagnosis of borderline personality disorder. The parents of six children had this diagnosis. Five (83%) of these six children had Pediatric Symptom Checklist scores above the cutoff, compared with two (18%) of the 11 children whose parents had other axis II diagnoses, and 14 (17%) of the 83 children whose parents had no axis II diagnosis ($\chi^2$=15.0, df=2, p<0.001).

Twenty-six of the children lived in single-parent homes. Eleven (42%) of these children had Pediatric Symptom Checklist scores above the cutoff, compared with 10 (14%) of the 74 children from intact homes ($\chi^2$=8.0, df=1, p<0.01).

Eight (38%) of the 21 children whose parents were in the lower occupational status group had Pediatric Symptom Checklist scores above the cutoff, compared with eight (21%) of the 38 children whose parents were in the middle group and five (14%) of the 37 children whose parents were in the higher status group ($\chi^2$=4.8, df=2, p<0.10).

### *Interview*

The parents of 98 of the 100 children (all but one of the children with Pediatric Symptom Checklist scores above the cutoff and one with Pediatric Symptom Checklist scores below the cutoff) agreed to be included in the pool of potential interview subjects. We selected for interview the parents of all of the remaining children who had Pediatric Symptom Checklist scores above the cutoff (20 children) and the parents of 20 of the children with Pediatric Symptom Checklist scores below the cutoff. The parents of 37 (93%) of the 40 children (19 with score above and 18 with scores below the cutoff on the Pediatric Symptom Checklist) actually completed the interview. Interview subjects did not differ from those not interviewed on any of the demographic variables or on diagnosis, with one exception: interview subjects were significantly more likely to have borderline personality disorder (six of these patients versus none of those who were not interviewed had this diagnosis) ($\chi^2$=8.2, df=1, p<0.01). Since we attempted to interview the parents of all children with Pediatric Symptom Checklist scores above the cutoff, this finding was due to the particularly high rate of Pediatric Symptom Checklist scores above the cutoff in children of parents with the diagnosis of borderline personality disorder.

Of the 37 children whose parents were interviewed, 24 (65%) had received psychiatric treatment at some point in their lives: 17 of the 19 children with Pediatric Symptom Checklist scores above the cutoff and seven of the 18 with scores below the cutoff ($\chi^2$=8.3, df=1, p<0.004). Twelve of the children with Pediatric Symptom Checklist scores above the cutoff were currently in treatment, and an additional five had seen a mental health professional in the past. Eight of the 19 children had received psychotropic medication, seven had been hospitalized for psychiatric treatment, and four were currently in psychiatric institutions. None of the children with Pediatric Symptom Checklist scores below the cutoff had been hospitalized, institutionalized, or received psychotropic medication.

From the standpoint of unmet mental health needs, although 17 of the 19 children who scored above the Pediatric Symptom Checklist cutoff had seen a mental health professional at some point, five of these children were not currently in treatment, and another two children with scores above the cutoff had never received any professional help. Thus, seven out of 19 of the children who were identified as being at risk by the Pediatric Symptom Checklist were not currently receiving psychiatric treatment.

## DISCUSSION

The children of psychiatric patients are at high risk for psychiatric disorder and psychosocial dysfunction. The findings of this study suggest that the Pediatric Symptom Checklist can serve as a screening instrument to alert general psychiatrists who may not have the time, training, or inclination to evaluate the psychopathology and functioning of each of their patient's children.

According to our experience in pediatric settings, the Pediatric Symptom Checklist performed as expected. The questionnaire was accepted by 90% of the parents in the waiting room and was completed and scored without difficulty in approximately 5 minutes.

The rate of 21% for scores above the cutoff on the Pediatric Symptom Checklist was significantly higher than that found in comparable pediatric groups. However, the rate of dysfunction among children in the current study group was lower than the rates reported for the children of psychiatric patients in other studies (16, 17). This discrepancy may be explained by the relatively high rate of anxiety disorders and low rate of psychotic disorders in this group of parents, their relatively high socioeconomic status, and our psychopharmacology clinic's close working relationship with the child psychiatric clinic. The study further highlighted that psychosocial dysfunction and case finding in this group of children was more likely when parents were single, of low socioeconomic status, or had the diagnosis of a personality (especially borderline) or mood disorder.

From the perspective of screening children to identify those in need of further evaluation, more than a third of the children with Pediatric Symptom Checklist scores above the cutoff were currently not in treatment, although most had seen a mental health professional at some point. We expect the rate of dysfunction in the children of patients would be even higher in other psychiatric settings where child psychiatric services are not as integrated and readily available as they are in the teaching hospital that was the site of our current study.

Future research is needed to elaborate these initial findings, particularly with respect to obtaining more in-depth psychiatric assessments of the children and identifying specific patterns of parental reporting. In psychiatric practices with higher percentages of severely ill patients, parents may have difficulty completing the Pediatric Symptom Checklist or reporting accurately, and thus the results of screening may not be as reliable or valid as in study groups like the present one.

Despite the need for further research, the Pediatric Symptom Checklist does appear to offer a brief, practical approach to identifying dysfunctional children of psychiatric patients. The Pediatric Symptom Checklist can help general psychiatrists become aware of and address the parenting role of their patients as well as the psychiatric needs of their patients' children. Given the increasing emphasis on cost containment and highly focused treatment, we will need innovative approaches to appreciate the patient's many facets, especially his or her role as a parent.

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**APPENDIX 1. Pediatric Symptom Checklist**

Please mark under the heading that best fits your child:

| Symptom | Never | Sometimes | Often |
|---|---|---|---|
| 1. Complains of aches or pains | ___ | ___ | ___ |
| 2. Spends more time alone | ___ | ___ | ___ |
| 3. Tires easily, little energy | ___ | ___ | ___ |
| 4. Fidgety, unable to sit still | ___ | ___ | ___ |
| 5. Has trouble with a teacher | ___ | ___ | ___ |
| 6. Less interested in school | ___ | ___ | ___ |
| 7. Acts as if driven by a motor | ___ | ___ | ___ |
| 8. Daydreams too much | ___ | ___ | ___ |
| 9. Distracted easily | ___ | ___ | ___ |
| 10. Is afraid of new situations | ___ | ___ | ___ |
| 11. Feels sad, unhappy | ___ | ___ | ___ |
| 12. Is irritable, angry | ___ | ___ | ___ |
| 13. Feels hopeless | ___ | ___ | ___ |
| 14. Has trouble concentrating | ___ | ___ | ___ |
| 15. Less interest in friends | ___ | ___ | ___ |
| 16. Fights with other children | ___ | ___ | ___ |
| 17. Absent from school | ___ | ___ | ___ |
| 18. School grades dropping | ___ | ___ | ___ |
| 19. Is down on him or herself | ___ | ___ | ___ |
| 20. Visits doctor with doctor finding nothing wrong | ___ | ___ | ___ |
| 21. Has trouble sleeping | ___ | ___ | ___ |
| 22. Worries a lot | ___ | ___ | ___ |
| 23. Wants to be with you more than before | ___ | ___ | ___ |
| 24. Feels he or she is bad | ___ | ___ | ___ |
| 25. Takes unnecessary risks | ___ | ___ | ___ |
| 26. Gets hurt frequently | ___ | ___ | ___ |
| 27. Seems to be having less fun | ___ | ___ | ___ |
| 28. Acts younger than children his or her age | ___ | ___ | ___ |
| 29. Does not listen to rules | ___ | ___ | ___ |
| 30. Does not show feelings | ___ | ___ | ___ |
| 31. Does not understand other people's feelings | ___ | ___ | ___ |
| 32. Teases others | ___ | ___ | ___ |
| 33. Blames others for his or her troubles | ___ | ___ | ___ |
| 34. Takes things that do not belong to him or her | ___ | ___ | ___ |
| 35. Refuses to share | ___ | ___ | ___ |

# Determining Disability Due to Mental Impairment: APA's Evaluation of Social Security Administration Guidelines

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*Objective: APA evaluated the Social Security Administration's (SSA's) medical standards and guidelines for determining disability due to mental impairment to determine how well the standards and guidelines operationalize the statutory definition of disability in a manner consistent with current psychiatric practice. Method: Seventy-two psychiatrists were trained in one of two procedures: those in the sequential evaluation condition were trained in the process and forms used by the SSA's reviewing medical consultants, and those in the statutory definition condition were trained in the statutory definition of disability and application of clinical judgment according to this standard. Decisions regarding claimants' ability or inability to work were recorded on an instrument designed for the study. Each condition consisted of 12 panels of three members. They reviewed 732 actual claims for disability benefits. The panelists reviewed claims independently, then rendered panel judgments. Each claim was reviewed by one panel in each condition. Results: The proportion of agreement between conditions for panel decisions (0.77) was higher than chance agreement (kappa= 0.46). The high level of agreement on claims judged to have good medical evidence and on which confident decisions were made (proportion of agreement=0.96, kappa=0.78) suggests that disagreements largely reflected ambiguities in application of the standards and guidelines to more complex cases or those with inadequate information. Conclusions: The SSA's revised medical standards and guidelines reflect clinical decisions about ability to work based on the statute and, with procedural modifications, should be retained. The SSA should be involved in further systematic studies to develop a field of scientific inquiry into disability and psychiatric disorders.*

(Am J Psychiatry 1991; 148:1037–1043)

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The Social Security Administration (SSA) soon will issue revised medical standards and guidelines for use in determining disability due to mental impairment under the Supplemental Security Disability Insurance (SSDI) and Supplemental Security Income (SSI) programs, Titles II and XVI, respectively, of the Social Security Act. The issuance of finalized procedures by the SSA will mark the culmination of a more than decade-long process undertaken to ensure that 1) the basis on which disability determination decisions are made reflects contemporary mental health diagnostic and therapeutic practices and 2) the disability review process is consistent with the legal definition of disability.

A need for psychiatrists and other mental health professionals to be familiar with the revised medical standards and guidelines is dictated, first, by the needs of persons with chronic mental illness. Familiarity with SSA procedures is essential given the responsibility increasingly being assumed by psychiatrists for the care and management of chronic patients (1). The revision also is important to psychiatrists in light of the role

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that organized psychiatry has played over the past decade in advocating improvement of the standards and guidelines and, more critically, in evaluating the SSA's proposed revision and suggesting further refinements.

## STUDY BACKGROUND

The SSA developed and, in 1985, issued interim procedures for determining disability due to mental impairment in the wake of the abrupt disqualification for SSI and SSDI benefits of hundreds of thousands of disabled persons in the late 1970s and early 1980s (2). Stung by public and legislative backlash to the paring of disability rolls, which was felt disproportionately and often tragically by mentally ill individuals, the SSA had invited diverse professional, citizen advocacy, and governmental organizations in the mental health field to participate in revising the standards and guidelines. APA was represented in this consultative collaboration, as were the other major mental health professions, the Mental Health Law Project, and the National Institute of Mental Health.

Subsequently, the SSA awarded a contract to APA to conduct an independent, scientific assessment of the revised methods and standards. This was the first time the agency had commissioned an evaluation of SSA medical standards and guidelines by an outside organization.

The study was designed to ascertain the accuracy with which the newly revised medical standards and guidelines used by the agency's medical consultants operationalize the statutory definition of disability due to mental impairment and their consistency with contemporary psychiatric knowledge and practice patterns. Within this broad study objective, the researchers sought to identify and characterize cases found difficult to evaluate with the medical standards and guidelines, pinpoint the specific cause or source of the difficulty, and suggest ways of minimizing difficulties.

## LISTINGS OF IMPAIRMENTS

The nucleus of the revised standards and guidelines is the "listings," which consist of eight diagnostic categories, each containing two or more sets of criteria designed to substantiate the existence of a medically determinable mental impairment (the A criteria) and to assess resultant functional limitations on an individual's ability to work (the B or C criteria).

The eight diagnostic categories, which supplant four in the prior version of the listings, are organic mental disorders; schizophrenic, paranoid, and other psychotic disorders; affective disorders; mental retardation and autism; anxiety-related disorders; somatoform disorders; personality disorders; and substance addiction disorders. The last category, substance addiction disorders, was not assessed in the APA study.

In addition to expanding the array of diagnoses, the revised listings were an improvement insofar as the clinical signs and symptoms (i.e., the A criteria), based on the then recently published *DSM-III*, were considerably more clearly defined and easily observed than they had been previously. An individual must have either the signs or symptoms identified by the SSA as defining the disorders outlined in the A criteria or their medical equivalent.

The A criteria disorder must result in limitations of functioning as defined by the B (or C) criteria. The B criteria encompass four areas of functioning: 1) activities of daily living, such as cleaning, shopping, grooming, paying bills, and maintaining a residence; 2) social functioning, at work and in the patient's personal life; 3) concentration, persistence, and pace in the completion of tasks that are commonly part of work; and 4) deterioration or decompensation in work or work-like settings that may result in the individual's either withdrawing from the situation or experiencing an exacerbation of signs and symptoms of illness and, in turn, a regression in the other domains.

The revised B criteria emphasize work-related limitations and relax the earlier requirement that limitations must be found in *all* areas of functioning. For a patient's condition to satisfy the degree of severity required for a determination of disability, marked difficulty in two or three of the B criteria must be evident over time.

The revised listings also provide C criteria, which take into consideration the effects of structured residential arrangements and/or medications that ameliorate clinical symptoms and offer a false picture of capacity for gainful employment. Participation in the labor force can upset the delicate balance of stable functioning made possible by the supportive residence or medication.

The Psychiatric Review Technique Form is used by the SSA's reviewing medical consultants to record the assessment of the A, B, and C criteria. Regulations mandate the use of this form, and it was evaluated in the APA study.

## METHOD

The study consisted of three components. The first examined the compatibility of the SSA's revised medical standards and guidelines with the statutory definition of disability, and it provided the bulk of the empirical data generated by the study. In component 2, questionnaires elicited from study participants qualitative data regarding their impressions of the medical review portion of the disability determination process. Component 3 consisted of an intensive examination of apparent sources of the incompatibility identified in component 1, thus permitting the development of recommendations for improving the SSA standards and guidelines. The focus of this report is component 1; components 2 and 3 are discussed only to the extent necessary to clarify the findings or implications of component 1 or to explain the basis for APA's recommendations to the SSA.

Component 1 was designed to yield a quantitative assessment of the compatibility of the SSA's medical standards and guidelines with the definition of disability contained in Social Security Act Section 223(d)(1), i.e., "the inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment which can be expected to result in death or which has lasted or can be expected to last for a continuous period of no less than 12 months."

The compatibility of the SSA's medical standards and guidelines with this definition of disability was assessed by 72 psychiatrists who were a demographically and professionally heterogeneous sample of the APA membership and were recruited from five cities. Each psychiatrist was assigned to one of two study conditions. One, the sequential evaluation condition, is the process followed by the SSA's reviewing medical consultants in actual casework. Participants assigned to the sequential evaluation condition were familiarized with the statutory definition of disability, then trained to use SSA's medical standards and guidelines (i.e., the listings and Psychiatric Review Technique Form) in the agency's standard, multistep assessment. Psychiatrists in the second condition, the statutory definition condition, reviewed claims on the basis of their knowledge of the characteristics of and limitations associated with the disorders suffered by the claimants. Training consisted of in-depth discussions of the claimants' impairments and functional limitations and whether they were or were not considered disabled according to the law. The only constraint on the professionally inspired judgments of the participants in the statutory definition condition was the requirement that they apply to claims the statutory definition of disability, with which they had been familiarized during training. Generic forms, as opposed to the Psychiatric Review Technique Form, were used to document their decisions.

Psychiatrists in both study conditions were instructed in the use of the Clinical Disability Severity Rating (CDSR), which was specially designed for the study, and in the study's panel procedures, which will be described.

### Clinical Disability Severity Rating

The CDSR was developed for the study to document the raters' clinical judgments of a given claimant's ability or inability to work on the basis of mental condition and, in turn, to better understand disagreements between study conditions. Once the existence of a mental impairment had been determined, study participants used the CDSR to make a dichotomous decision as to whether or not a claimant could work. A 10-point summary rating designed to reflect the medical components of the statutory definition of disability, the CDSR is scaled from $-5$ (unable to work) to $+5$ (able to work); no zero point permits a dichotomous rating, with negative scores signifying inability to work. An "N" rating point permitted psychiatrists to register their decisions that a claimant did not have a medically determinable impairment with a 12-month duration. A companion confidence rating allowed the psychiatrists to scale the confidence with which they made their CDSR judgments.

Psychiatrists in the sequential evaluation condition scored claimants on the CDSR only after completion of their ratings with the SSA's standards and guidelines.

### Panel Process

In component 1, all training and research participation occurred within the context of condition assignment and panel membership. The 36 psychiatrists assigned to each condition were further grouped into 12 three-member panels. The rationale for the panels was that they would help participants make judgments reflecting the "view of currently practicing American psychiatrists." During training, individuals were guided to identify with a panel standard rather than individual standards alone. The panels were intended to increase reliability and reduce idiosyncratic judgments.

Constant rotation of panel assignments during training ensured that all participants in the project were familiar with the personal and professional attitudes and perspectives of their colleagues. Upon the completion of training, however, 24 panels were created that were maintained for the duration of component 1; each was structured to be heterogeneous and to avoid former collegial relationships among panelists.

### Claims

A sample of 732 initial claims for disability benefits were provided for assessment in the study. These claims had been filed by adults, had passed quality assurance review by SSA regional offices, and had been reviewed by the SSA under the revised standards for mental impairments. Identifying characteristics of the claimants were removed by the SSA to maintain confidentiality.

Each claim was reviewed by one panel in each study condition, a total of six psychiatrists. When all 732 claims had been reviewed, the data were contained on 4,392 study forms (2,196 forms from each study condition). Upon receipt of the forms, project staff reviewed each for completeness and accuracy and conferred with the submitting psychiatrist to correct problems.

### Analytic Methods

The CDSR was used to measure overall agreement between the sequential evaluation and statutory definition conditions for the 732 claims reviewed in component 1. In the analyses discussed here, two different methods of assessing the concept of CDSR agreement were used to address two areas of research interest: 1)

**TABLE 1. Agreement on 732 Disability Claimants' Ability to Work[a] of Psychiatrists Using Social Security Administration Procedures (Sequential Evaluation, N=36) and Those Directly Applying Statutory Definition of Disability (N=36)**

| | Judgment of Individual Psychiatrists | | Consensus of Three-Member Panels | |
|---|---|---|---|---|
| Type of Agreement | Proportion of Agreement | Kappa | Proportion of Agreement | Kappa |
| Within conditions | | | | |
| Sequential evaluation | 0.76 | 0.41 | | |
| Statutory definition | 0.75 | 0.42 | | |
| Between conditions | 0.72 | 0.36 | 0.77 | 0.46 |

[a]Judgments about ability to work made with the Clinical Disability Severity Rating.

between-condition agreement based on the decisions of individual panelists and 2) between-condition agreement based on panel consensus decisions.

The CDSR was used to assess agreement between the two conditions. Panel agreement was defined as agreement by a majority of the three panelists in each condition about whether or not the claimant was able to work. For the sequential evaluation condition, the decision was based on an interpretation of the law as specified in the SSA listings, regulations, and procedures. For the statutory definition condition, the decision was based on a direct interpretation of the law.

## RESULTS

Application of the two analytic methods to the 732 claims yielded the summary statistics for CDSR agreement provided in table 1. That between-condition agreement—as obtained through 1) independent ratings by individual panelists before panel discussions and 2) panel ratings—is higher than would be expected by chance is seen in the respective kappa values for this analysis, 0.36 and 0.46. The higher level of agreement by the panels reflects the protection afforded by panels against the errors and idiosyncratic biases associated more with individual judgments.

The top of table 2 presents the distribution of panel decisions for the two study conditions.

### *Disagreement Between Study Conditions*

A model was developed to identify specific potential sources of error that led to disagreements in clinical judgments about claims. Eliminating claims for which between-condition disagreement was attributed to causes other than the medical standards and guidelines yielded a subset of claims used in the intensive reexamination (component 3) conducted to specify problems in the standards and guidelines and to develop recommendations for improving the listings and the Psychiatric Review Technique Form.

The model posited three potential sources of error. The first source was claims that were inherently difficult. A claimant may be on the boundary, for example, of "able" and "not able" to work, or the evidence contained in a claim folder might be ambiguous or contradictory. In instances in which the medical evidence can be interpreted logically in two ways, the judgment might be "able to work" half the time and "not able" the other half, regardless of the number of reviews or the accuracy of assessment standards.

A second possible source of disagreement is the complexity of the sequential evaluation process itself. A reviewer may miss a piece of evidence or forget a seldom-used, detailed instruction for the Psychiatric Review Technique Form.

Finally, the medical standards and guidelines may account for discrepancies between the two study conditions. If the standards and guidelines are too lenient or too restrictive in operationalizing the statute, they may bias clinical judgment regarding a claimant's ability to work. Another problem might be ambiguity of the standards and guidelines—for example, failure to specify which 12-month period should be considered in assessing the impact of mental impairments on the claimant's ability to work.

Although it was not possible to distinguish cleanly the effects of these factors in each ambiguous claim, estimating the level of panel agreement between conditions for claims judged relatively free of ambiguity helped to eliminate from analytic consideration claims for which inherent difficulty seemed the most likely source of error. Basing the analysis on the panel majority CDSR decisions minimized the impact of ambiguities caused by individual panelist error. The disagreement between conditions remaining at this point was assumed to reflect the inherent difficulty of evaluating certain claims and/or biases or weaknesses in the medical standards and guidelines.

Three indicators based on the panelists' assessments for each claim were used to screen out claims with apparent ambiguities. The indicators were 1) relatively low confidence in the CDSR score, 2) a relatively low rating of the overall medical evidence, and 3) marginal CDSR scores (i.e., rated +1 or −1 by a majority of panelists). Claims were grouped according to these indicators independently of whether the psychiatrists in the two conditions agreed.

The agreement between study conditions for the remaining claims, which all had relatively high confidence ratings, good evidence ratings, and nonmarginal CDSR ratings, is shown in the lower half of table 2. Within these unambiguous claims (N=211), the participants in the two study conditions disagreed on only nine claims (4%). The high level of agreement between conditions on ratings of "able" and "not able" to work at both the individual and panel levels suggests that the disagreements between conditions can be explained largely by ambiguities inherent in the claims. If the standards and guidelines led to disability judgments that were markedly different from those based on direct application of the statute, much more dis-

**TABLE 2. Disability Claimants Judged Able or Not Able to Work[a] by Panels of Psychiatrists Using Social Security Administration Procedures (Sequential Evaluation, N=36) and Those Directly Applying Statutory Definition of Disability (N=36)**

| | Sequential Evaluation Rating | | Proportion of Agreement | | Kappa | |
|---|---|---|---|---|---|---|
| Statutory Definition Rating | Able to Work | Not Able to Work | Actual | Expected by Chance | Value | SD[b] |
| Overall | 182 | 550 | 0.77 | 0.58 | 0.46 | 0.03 |
| Able to work (N=248) | 132 | 116 | | | | |
| Not able to work (N=484) | 50 | 434 | | | | |
| Relatively unambiguous claims | 20 | 191 | 0.96 | 0.81 | 0.78 | 0.07 |
| Able to work (N=25) | 18 | 7 | | | | |
| Not able to work (N=186) | 2 | 184 | | | | |

[a] Judgments about ability to work made with the Clinical Disability Severity Rating.

[b] Approximate standard error of kappa (3).

agreement would have been found between the two study conditions.

The findings do not rule out the possibility, however, that improvements could be made in the standards and guidelines which would result in more unambiguous claims.

*Agreement on Specific Categories of Impairment*

Agreement was examined for the various diagnostic categories of mental impairment (table 3). Considerable variability was found, although the criteria for functional limitation are nearly identical for most categories. A very low kappa was found for category 12.07 (somatoform disorders). The low number of claims judged in this category, however, prohibits generalizations or interpretations. Of the remaining categories of impairment, category 12.04 (affective disorders) had the least agreement between conditions, although not so low as to suggest a major deficiency in the standards and guidelines for this category. Plausible explanations for the somewhat lower agreement include 1) the fundamentally recurrent nature of affective disorders, which makes evaluation difficult, even according to the statutory definition, and 2) the greater heterogeneity likely to be found among claimants diagnosed as having affective disorders.

*Characteristics of Difficult Claims*

Table 4 summarizes the results of one of the principal objectives of the study—to identify factors associated with difficulty in evaluating a claim. Both the proportion of disagreements and odds ratio (the odds of a disagreement for claims in a given category, compared to all other claims) associated with each of several variables are presented.

The variables most strongly associated with disagreement between conditions were the panelists' direct ratings of claim difficulty: marginality of CDSR rating (i.e., −1 or +1), low confidence in the CDSR score, and low quality of the medical evidence. The finding that CDRS marginality accurately predicts disagreement essentially validated what the instrument was designed to do—assess inherent claim difficulty and thereby predict disagreement on claims. Other variables found to increase substantially the probability of disagreement included the presence of a nonpsychiatric disorder, an onset of impairment less than 12 months before the review, being female, and a medical disposition of "RFC necessary" (i.e., assessment of work-related capacities in an individual with a severe impairment who cannot be judged disabled on the basis of the listings alone).

**TABLE 3. Association Between Diagnosis and Agreement on Disability Claimants' Ability to Work[a] of Psychiatrists Using Social Security Administration Procedures (N=36) and Those Directly Applying Statutory Definition of Disability (N=36)**

| Diagnostic Category | Category Number | Number of Claims | Proportion of Agreement | Kappa |
|---|---|---|---|---|
| Organic mental disorders | 12.02 | 82 | 0.87 | 0.48 |
| Schizophrenic, paranoid, and other psychotic disorders | 12.03 | 123 | 0.86 | 0.41 |
| Affective disorders | 12.04 | 227 | 0.72 | 0.36 |
| Mental retardation and autism | 12.05 | 139 | 0.75 | 0.43 |
| Anxiety-related disorders | 12.06 | 52 | 0.85 | 0.68 |
| Somatoform disorders | 12.07 | 17 | 0.65 | 0.16 |
| Personality disorders | 12.08 | 92 | 0.73 | 0.44 |

[a] Judgments about ability to work made with the Clinical Disability Severity Rating.

## DISCUSSION

The APA study was designed to assess, from the perspective of practicing psychiatrists, the consistency of the SSA's medical standards and guidelines and the statutory definition of disability. The two study conditions operationalized the statutory definition in different ways, and the quantitative and qualitative data obtained allowed examination of inconsistencies between the two conditions. The proportion of agreement between the two study conditions, based on panel CDSR ratings, was 0.77; the kappa was 0.46.

**TABLE 4. Association Between Study Variables and Disagreement on 732 Disability Claimants' Ability to Work[a] of Psychiatrists Using Social Security Administration Procedures (N=36) and Those Directly Applying Statutory Definition of Disability (N=36)**

| Variable | Proportion of Disagreement | Odds Ratios ≥1.0 |
|---|---|---|
| Panelist ratings of claim difficulty | | |
| Marginality of CDSR | | |
| Marginal (+1 or −1) | 0.42 | 7.3[b] |
| Nonmarginal | 0.09 | |
| Confidence in CDSR rating | | |
| Low | 0.33 | 3.4[b] |
| High | 0.12 | |
| Quality of medical evidence | | |
| Relatively low | 0.30 | 2.4[b] |
| Relatively high | 0.15 | |
| Psychiatric Review Technique Form | | |
| Medical disposition | | |
| RFC necessary[c] | 0.41 | 3.0[b] |
| Impairment not lasting 12 months | 0.33 | |
| No medically determinable impairment | 0.21 | |
| Meets or equals listings | 0.18 | |
| Impairment not severe | 0.17 | |
| Category of impairment | | |
| 12.07 (somatoform disorders) | 0.35 | 1.9 |
| 12.04 (affective disorders) | 0.28 | 1.6[b] |
| 12.08 (personality disorders) | 0.27 | 1.3 |
| 12.05 (mental retardation and autism) | 0.25 | 1.2 |
| 12.06 (anxiety-related disorders) | 0.15 | |
| 12.03 (schizophrenic, paranoid, and other psychotic disorders) | 0.14 | |
| 12.02 (organic mental disorders) | 0.13 | |
| Clinical variables | | |
| Presence of notable nonpsychiatric disorder | | |
| Yes (N=122) | 0.34 | 2.1[b] |
| No | 0.20 | |
| Onset of impairment | | |
| Less than 12 months before review | 0.33 | 1.8[b] |
| More than 12 months before review or never | 0.22 | |
| Work history | | |
| More than 4 years or eligible for Social Security Disability Insurance | 0.24 | 1.2 |
| 3 months to 4 years | 0.24 | 1.1 |
| Less than 3 months | 0.18 | |
| Notable alcohol or drug abuse | | |
| Yes[d] | 0.24 | 1.1 |
| No | 0.23 | |
| Demographic variables | | |
| Age (years) | | |
| 25 to 54 | 0.25 | 1.5 |
| 55 or older | 0.22 | |
| Less than 25 | 0.16 | |
| Sex | | |
| Female | 0.27 | 1.8[b] |
| Male | 0.18 | |

[a] Judgments about ability to work made with the Clinical Disability Severity Rating (CDSR).

[b] Odds of disagreement statistically greater than chance.

[c] "RFC" refers to the Mental Residual Functional Capacity Assessment, which is used when a severe mental impairment does not meet or equal a listing; the form documents a clinical assessment of a mentally impaired individual's work-related capacities.

[d] N=46.

In determining disability based on mental impairment, it is unreasonable to expect 100% agreement. Disability typically is a complex medical, psychological, and social concept, difficult to define and complicated to operationalize for programmatic and administrative purposes (4–6). The task of developing standards and guidelines to assist in documenting the clinical determination of disability is intricate. Further, disability decisions are made by psychiatrists with diverse clinical training, orientation, and professional experience. In spite of these apparent barriers, the agreement was good.

For this study, the SSA did not establish a specific kappa value as minimally acceptable for programmatic purposes. Furthermore, we are unaware of prior studies reporting kappa statistics on clinical agreement about disability based on mental and other medical disorders. Thus, it is useful to place this study's kappa of 0.46 within the context of other kappa statistics that measure clinical agreement.

The kappa statistics from the field trials of the *DSM-III* axis I diagnostic categories, which most closely resemble the listings, ranged from 0.42 to 0.83 (*DSM-III*, appendix F). These kappas represent the reliability of diagnostic classification of psychiatric cases from a clinical sample.

Kappas reported for diagnostic agreement in other areas of medicine encompass diverse categories of disorders and methods of assessment, and they are quite variable. One in current major clinical epidemiological text (7) gives a kappa of 0.33 for abnormal ophthalmological findings, and another (8) gives 0.55 for clinical ratings of retinopathy, 0.51 for the absence of a dorsalis pedis pulse, 0.50 to 0.62 for signs of chronic air flow obstruction, 0.39 for ratings of peripheral blood flow film for iron deficiency, 0.67 for assessment of mammograms for suspected malignancy, and 0.30 for reading exercise cardiograms of potential bypass surgery patients.

The statistical literature on clinical agreement includes the statement that "values [between 0.40 and 0.75] are generally taken to represent fair to good agreement beyond chance" (9). The kappa statistic for this study may be viewed, conservatively, as moderate and well within the range of the kappas for clinical agreement for well-developed current medical practice.

Agreement notwithstanding, the summary measures indicate a considerable amount of disagreement between the two study conditions. For APA to provide the SSA with useful feedback, a key question was how much of the disagreement was attributable to the SSA's medical standards and guidelines. The 23% of cases in which there was disagreement constituted a useful data set for this purpose.

The high level of agreement for claims identified as relatively unambiguous (proportion=0.96, kappa=0.78) suggests that for claimants whose ability to work is not marginal and for whom the medical evidence is adequate, the standards and guidelines work extremely well, as reflected in psychiatrists' decisions based directly on the statute. The near disappearance of disagreement between study conditions suggests that inherent difficulty, not the standards and guidelines, played a major role in the disagreement between study conditions. Moreover, when the panelists were asked to suggest how they would improve the procedures they had been trained to apply, none suggested a need for extensive changes; rather, they tended to propose relatively minor refinements. The most critical new issue raised in component 3 (i.e., the examination of apparent sources of incompatibility between conditions) involved the difficulty in formally establishing the date of onset of the impairment that was being clinically assessed, as required by the SSA; this date conceivably could precede the period of disability under review. Unable to document a decision about the period of review on the Psychiatric Review Technique Form, psychiatrists found that they were rating different periods, sometimes causing differences in clinical opinion; aligning the time frame led to more consistent judgments.

On the basis of all of the evidence, we conclude that the basic construct of the medical standards and guidelines reflects clinical decisions about ability to work based on the statute and, as a process, should be retained. We also conclude that the deficiencies in the medical standards and guidelines identified in the APA study can be addressed through modifications. The following recommendations are offered, among others detailed in the study report.

1. The SSA should develop clearer instructions for defining the period of disability under review.

2. The SSA should continue efforts to improve the collection of medical and other evidence and, particularly, introduce a standardized federal form to be distributed for use by treating psychiatrists and psychologists and by consultative examiners for the collection of medical evidence for all claims based on mental impairment(s). Such a form would include a current mental status examination.

3. The SSA should build on initiatives taken in this study to identify and provide special evaluation of difficult claims and, specifically, further explore the use of the CDSR and other study variables to develop a flagging system for these claims in the SSA system. The agency should work with the field to develop alternative methods for the review of identified difficult claims, such as a peer review system or the use of panels.

4. The SSA should develop standardized comprehensive training programs and manuals for the reviewing medical consultants in the Disability Determination Service; this task should be contracted to an outside organization which would collaborate with the SSA to assure that current medical knowledge and training materials are incorporated into the program.

5. The SSA should develop and conduct a systematic series of studies and research development activities in collaboration with academic institutions and other organizations, although no single study is ever the definitive evaluation of an issue or a process. The listings and the Psychiatric Review Technique Form deserve continued evaluation within the SSA and by outside organizations. Furthermore, the SSA can and should play an essential role in developing a field of scientific inquiry into disability and psychiatric disorders.

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# Cost Offset From a Psychiatric Consultation-Liaison Intervention With Elderly Hip Fracture Patients

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*Objective: The authors hypothesized that psychiatric liaison screening of elderly patients with hip fractures would shorten the average length of hospital stay and increase the proportion of patients who returned home after discharge. Method: The study was performed at Mount Sinai Medical Center in New York and Northwestern Memorial Hospital in Chicago. The subjects were 452 patients 65 years or older who were consecutively admitted for surgical repair of fractured hips. During a baseline year the patients received traditional referral for psychiatric consultation. During the experimental year all the patients at Mount Sinai and the patients on one Northwestern unit were screened for psychiatric consultation. Results: The patients who received psychiatric liaison screening had a higher consultation rate than those who received traditional consultation. The rates of* DSM-III *disorders in the experimental year were 56% at Mount Sinai and 60% at Northwestern. The mean length of stay was reduced from 20.7 to 18.5 days at Mount Sinai and from 15.5 to 13.8 days at Northwestern, resulting in reductions in hospital costs ($647/day) of $166,926 and $97,361, respectively. Fees generated from Medicare service delivery could have paid for the $20,000 psychiatric intervention cost at each site. There was no difference, however, between the two years in the discharge placement of patients. Conclusions: Admission psychiatric liaison screening of elderly patients with hip fractures results in early detection of psychiatric morbidity, better psychiatric care, earlier discharge, and substantial cost savings to the hospital.*

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Studies suggest that psychosocial interventions in health care settings improve patient well-being and the quality of care (1, 2), and evidence suggests that these interventions can help reduce medical costs as well (3–6). In this paper we report findings on the effects of a psychiatric intervention on the costs of health care for elderly hip fracture patients in two diverse teaching hospitals.

There is a strong indication that psychiatric and psychosocial variables are important in general hospital care. Lipowski (7) reported that more than one-half of all hospitalized and medically ill patients manifest psychological dysfunction in conjunction with medical illness and that these problems inevitably detract from effective medical care. Other authors (8, 9) have estimated that one-third to one-half of hospitalized patients have primary psychiatric morbidity. Regier et al. (10) reported that more than one-half of the patients with psychiatric morbidity are seen exclusively in the general health care system, rather than by mental specialists. More specifically, studies have provided data on the relationship between psychosocial factors and the length of hospital stays. Zimmer (11) found that for more than 2,500 patients, 11.8% of all hospital days could not be attributed to medical need. Glass et al. (12) reported that for 363 hospitalized medical/surgical patients, 18% of the hospital days were due to social rather than medical factors. Other researchers (13, 14) noted the importance of social factors in the decision to admit patients to the hospital, particularly for emergencies. Mumford et al. (15) found that a psy-

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chosocial intervention reduced the use of medical services, especially for inpatients and patients more than 55 years old.

Two studies of orthopedic patients (3, 4) demonstrated the potential for impressive cost savings. Boone et al. (4) reported a reduction in mean length of stay of 1.25 days after institution of an early social work intervention. This translated into a gross savings of approximately $54,000 for 187 patients over 6 months. The savings for elderly patients alone would have been still larger. Levitan and Kornfeld (3) compared the patients in an orthopedic ward before and after the introduction of a liaison psychiatrist. They demonstrated a 12-day reduction in the median length of stay (42 to 30 days), which translated into a $50,000 cost reduction over 6 months, more than offsetting the cost of the psychiatric intervention ($10,000). If placement in the patient's home, rather than a nursing home, was included in these authors' cost offset estimates, $197,000 was saved in the treatment of the patients on the intervention ward.

Although provocative, both of these studies suffered from serious methodological flaws. For example, no attempt was made to specify the psychosocial services provided to the nonintervention patients. The comparison baseline groups were contaminated, at least in part, by unspecified psychosocial interventions. Levitan and Kornfeld used the patients on the same unit before the psychiatric intervention as their "control" group. Consequently, other factors could explain the results (e.g., changes in staffing or attending physicians, policy shifts, alterations in medical/surgical procedures, differences in the patients' health status or the availability of homes to go to) (16). Since the distribution of lengths of stay is almost always skewed to the right, differences in means may be misleading without proper data transformations (e.g., logarithmic).

Other methodological confounds that may have influenced Levitan and Kornfeld's important study are the lack of 1) randomized sampling techniques, 2) inclusion criteria, 3) reliable and valid measures, 4) raters blind to the hypotheses about the intervention, 5) sufficiently long observation periods, 6) information about severity of disease state, 7) specification of psychosocial disability, 8) delineation of the intervention and measurement of its intensity, 9) groups large enough to provide accurate estimates of population parameters, and 10) more comprehensive cost measures. Berk has argued persuasively for consideration of both direct and indirect costs and of who bears these costs: government, third-party payers, patients, or patients' families (unpublished paper, 1982).

This study was designed to take into account these methodological concerns. We hypothesized a reduction in the length of stay and an increase in the proportion of patients who returned home after discharge as a result of institution of a psychiatric liaison screen after a baseline year of traditional referral.

**TABLE 1. Demographic Characteristics of Elderly Patients With Hip Fractures**

| | Mount Sinai Hospital (N=264) | | Northwestern Memorial Hospital (N=200) | |
|---|---|---|---|---|
| Characteristic | N | % | N | % |
| Female | 210 | 79.5 | 161 | 80.5 |
| Married | 54 | 20.5 | 47 | 23.5 |
| Living alone | 134 | 50.8 | 128 | 64.0 |
| White | 233 | 88.3 | 182 | 91.0 |

## METHOD

The subjects were patients 65 years or older who were consecutively admitted to four orthopedic units for the surgical repair of fractured hips; one of the units was at the Mount Sinai Medical Center in New York City (N=264), and three were at Northwestern Memorial Hospital in Chicago (N=200). The mean± SD age of the patients at Mount Sinai was 83.7±8.4, and for those at Northwestern it was 80.3±8.3. Other demographic variables are shown in table 1. Informed consent was obtained from every patient who agreed to be studied and, if the patient's judgment was compromised such that he or she could not sign the permission statement required for surgery, a guardian, family member, or legal agent was asked to give permission for the patient to be studied.

Several instruments were used: a semistructured interview, a chart-review inpatient log, the Geriatric Depression Scale (17), the Arthritis Impact Measurement Scale (18), the Spielberger State-Trait Anxiety Inventory (19), the Horn Disease-Staging Evaluation (20), the Mini-Mental State (21), and the Singh index of bone density (22).

The primary outcome measures were 1) total length of stay, including the day of admission and the day of discharge regardless of hour, 2) total direct hospital charges plus per diem costs and charges by specific hospital cost centers, obtained from the hospitals' accounting departments, which maintained permanent records of all charges in 19 categories (e.g., laboratory, blood products, special-duty nursing, anesthesia, intensive care), and 3) placement of patient after discharge—home or health-related facility.

The design at Mount Sinai, which had only one orthopedic unit, was to compare two years on the same surgical inpatient unit. During the baseline year, psychiatric consultation was requested in the usual fashion by the orthopedic consultee. The next year an experimental psychiatric liaison intervention was instituted. The first year at Northwestern was also a baseline; only requested psychiatric consultations were offered. During the second year at Northwestern, one of three units (liaison unit A) provided the experimental psychiatric liaison intervention, and the other two units (control units B and C) acted as controls—offering psychiatric consultation only when requested.

**TABLE 2. Frequency of Psychiatric Consultation for Elderly Patients With Hip Fractures During Baseline Year and Year of Experimental Psychiatric Liaison Program**

| | Mount Sinai Hospital | | Northwestern Memorial Hospital | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Baseline Year | | | | Experimental Year | | | |
| | | | | Control Units | | | | Control Units | | |
| Patient Status | Baseline Year | Experimental Year | Liaison Unit A | B | C | Total | Liaison Unit A | B | C | Control Total |
| Admitted | 120 | 144 | 40 | 33 | 19 | 92 | 59 | 30 | 19 | 49 |
| Unwilling or unable[a] to complete study | 34 | 24 | 14 | 14 | 7 | 35 | 15 | 10 | 8 | 18 |
| Died | 2 | 6 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 0 |
| Completed study | 84 | 114 | 26 | 17 | 12 | 55 | 44 | 20 | 11 | 31 |
| Received consultation | | | | | | | | | | |
| Number | 12 | 114 | 1 | 0 | 1 | 2 | 36[b] | 2 | 1 | 3 |
| Percent of admitted patients | 10 | 79 | 3 | 0 | 5 | 2 | 61 | 7 | 5 | 6 |

[a] Unable to sign the consent form because of cognitive deficit, or family member was unavailable or unwilling to sign.

[b] Two of these patients were unwilling or unable to complete the study.

Control unit B was contiguous to liaison unit A, and the social worker was shared by both of them. Control unit C was in another section of the hospital, distant from liaison unit A and control unit B, and it had completely separate ward staff and an autonomous social worker. There was no structured exchange among units A, B, and C.

From July 1, 1987, through June 30, 1989, each patient was interviewed and evaluated within 72 hours of admission to the hospital but after surgical repair of the fractured hip; the patient was evaluated again at hospital discharge and 6 and 12 weeks after discharge. The number of subjects required to achieve the power necessary (0.80) for detection of significance in a difference in length of hospital stay of at least 2 days was 150 at both sites for each observation year ($p<0.05$).

The first year was a baseline on all four units. Psychiatric consultations were performed only for referred patients, and the psychiatrist had no other involvement with the orthopedic units. During the second year, a psychiatric liaison intervention was introduced on the Mount Sinai orthopedic unit and on unit A at Northwestern. The experimental psychiatric intervention consisted of the following components: 1) evaluation of every consenting patient by a psychiatrist and an offer of treatment for observed psychiatric morbidity if necessary, 2) weekly ombudsman rounds with a senior orthopedic attending physician, during which selected or difficult cases were discussed in detail by the attending orthopedic physician, social worker, nurse, physical therapist, and liaison psychiatrist in an attempt to achieve a multidisciplinary clinical treatment and discharge plan (23), 3) weekly nursing and discharge planning meetings to discuss cases in which the impediment to moving a patient to his or her home or to a nursing home was psychiatric morbidity, e.g., noncompliance, dementia, use of neuroleptic agents, or more global concerns about the patient's behavior, and 4) conferences with families and social workers as appropriate. The patient's family was counseled on the behavioral management of the patient, and particular attention was paid to their anxiety about dementia or psychotic thinking that was being treated with neuroleptics. Families and nursing homes expressed great anxiety about accepting responsibility for patients who manifested delusions or hallucinations or who were receiving antipsychotic medications.

A rating on the Singh bone density scale and postoperative stability were determined for every patient radiographically by the orthopedic surgeon after surgery, and these measures permitted a biological assessment of the bone and fracture status (22). The Horn severity of illness rating was determined on the basis of the patient's chart at discharge by a trained Horn rater (20). This permitted an objective assessment of other medical conditions and their complications. Where appropriate, statistical analyses were conducted with t tests for continuous variables and chi-square tests for categorical variables.

## RESULTS

As shown in table 2, at Mount Sinai the consultation rate was 10% in the baseline year and 79% in the experimental year. At Northwestern, during the baseline year the overall consultation rate for units A, B, and C was 2%, and in the experimental year it was 61% for unit A and 6% for units B and C. The psychiatric diagnoses of both the Mount Sinai and Northwestern patients are presented in table 3. Approximately one-half of the intervention groups at both institutions had diagnoses of organic mental disorder.

Table 4 shows the lengths of stay for the baseline and experimental years; patients whose lengths of stay were more than two standard deviations beyond the mean were omitted. The patients at Mount Sinai during the experimental year remained in the hospital an average of 2.2 days less than the patients during the baseline year, a statistically significant difference. If we

**TABLE 3. *DSM-III-R* Diagnoses of Elderly Patients With Hip Fractures Who Received Psychiatric Liaison Screening**

| Diagnosis | Mount Sinai Hospital (N=103[a]) |  | Northwestern Memorial Hospital (N=36) |  |
|---|---|---|---|---|
|  | N | % | N | % |
| Organic mental disorder | 58 | 56.3 | 17 | 47.2 |
| Major depression or dysthymia | 5 | 4.9 | 3 | 8.3 |
| Adjustment disorder, mixed | 0 | 0.0 | 2 | 5.6 |
| Adjustment disorder, depressed | 1 | 1.0 | 1 | 2.8 |

[a]Number of patients for whom data were available.

**TABLE 4. Length of Stay for Elderly Patients With Hip Fractures During Baseline Year and Year of Experimental Psychiatric Liaison Program[a]**

| Location | Baseline Year[b] |  |  | Experimental Year |  |  |
|---|---|---|---|---|---|---|
|  |  | Length of Stay (days) |  |  | Length of Stay (days) |  |
|  | N | Mean | SD | N | Mean | SD |
| Mount Sinai Hospital[c] | 114 | 20.7 | 9.1 | 136 | 18.5 | 8.5 |
| Northwestern Memorial Hospital[d] |  |  |  |  |  |  |
| Liaison unit A[e] | 39 | 15.5 | 4.7 | 55 | 13.8 | 4.1 |
| Control units | 48 | 13.9 | 3.8 | 51 | — | — |
| Unit B | 31 | 14.3 | 3.8 | 31 | 14.1 | 4.3 |
| Unit C[f] | 17 | 13.2 | 3.8 | 19 | 15.7 | 4.6 |

[a]Patients whose lengths of stay were more than two standard deviations beyond the mean are not included.
[b]Significant difference between baseline length of stay at Mount Sinai and that in Northwestern liaison unit (t=3.42, df=151, p≤0.05) and control units (t=4.96, df=160, p≤0.05).
[c]Significant reduction (t=1.97, df=248, p<0.05).
[d]Significant Time by Group interaction for Northwestern when the liaison unit was compared with both control units (F=4.03, df=1, 189, p≤0.05) and with control unit C (F=4.69, df=1, 125, p≤0.04).
[e]Nearly significant reduction (t=1.86, df=92, p=0.06).
[f]Nearly significant increase (t=1.77, df=34, p=0.10).

use an average per diem hospital cost of $647 (1987 dollars), this translates to a reduction in the total cost to the hospital of $178,572. (Average per diem costs are calculated by using standard Medicare cost reporting methods for medical/surgical patients and do not include the costs of intensive or cardiac care.) The marginal costs may be lower. However, the average daily cost estimate is conservative because it excludes the cost of intensive care. The psychiatrists at Mount Sinai made 272 patient visits to the intervention cohort, which could have generated $21,760 in fees ($80/visit) to offset the psychiatrist's salary of $20,000 for performing the consultations and liaison activities had this not been a funded research effort.

At Northwestern, the reduction in length of stay was 1.7 days for patients on liaison unit A (with outliers removed) (table 4). This reduction was significantly different from the change in length of stay for the control units and was associated with a reduction in costs of $97,361. Control unit B, which was contiguous to the liaison unit and shared a social worker and discharge planner with it, did not demonstrate a significant difference in length of stay between the two years (p=0.85). However, the isolated control unit C had an *increase* in the length of stay over the two years of the study (table 4). Because of the concern that death might affect the length of stay independent of any effects of the intervention, the results were recalculated after the patients who died were eliminated. The findings were identical to those without deaths removed.

To determine whether the reductions in length of stay were associated with reductions in psychiatric symptoms, we compared the patients' discharge depression and mental state scores after adjusting for initial levels and length of stay. At Mount Sinai, the liaison intervention was associated with a significant improvement in Mini-Mental State score (t=3.40, df=63, p<0.01). The adjusted mean±SD Mini-Mental State score at discharge was 22.71±5.81 during the experimental year and 19.92±7.79 during the baseline year. At Northwestern, the liaison intervention was associated with a significant reduction in the Geriatric Depression Scale score (t=3.20, df=92, p<0.01). The adjusted discharge depression score for the liaison unit patients was 11.9±2.0 during the experimental year and 12.75±2.7 during the baseline year. Fracture status, bone density, and the Horn ratings of severity of disease were similar in the experimental and baseline years at both Mount Sinai and Northwestern.

As shown in table 5, there was no significant difference in postdischarge patient placements between the baseline and experimental years at Mount Sinai or Northwestern (e.g., home versus home, home versus nursing home, nursing home versus nursing home). After discharge approximately one-half of the patients returned home, except for the patients in the control units at Northwestern, more of whom were transferred to rehabilitation hospitals. Among the patients at Mount Sinai, there was little difference in postdischarge placement between the baseline and experimental years. Among the patients on the liaison unit at Northwestern, there was a nonsignificant increase in nursing home placements and a similar decrease in placements to sites other than home, rehabilitation hospitals, and nursing homes.

## DISCUSSION

This baseline-intervention study in two disparate sites confirms the finding of Levitan and Kornfeld (3) that a structured psychiatric liaison program with elderly patients with hip fractures is associated with a shorter length of stay. The results also confirm the more global report by Mumford et al. (15) that a psychosocial intervention is associated with decreased

**TABLE 5. Placement After Discharge of Elderly Patients With Hip Fractures During Baseline Year and Year of Experimental Psychiatric Liaison Program**

| Placement After Discharge | Baseline Year | | | Experimental Year | | |
|---|---|---|---|---|---|---|
| | Admitted | Discharged | | Admitted | Discharged | |
| | | N | % | | N | % |
| Mount Sinai Hospital | 118[a] | | | 138[a] | | |
| Home | | 56 | 47.5 | | 60 | 43.5 |
| Rehabilitation hospital | | 16 | 13.6 | | 12 | 8.7 |
| Nursing home | | 41 | 34.7 | | 49 | 35.5 |
| Other | | 4 | 3.4 | | 8 | 5.8 |
| Northwestern Memorial Hospital | 92 | | | 108 | | |
| Liaison unit | 40 | | | 59 | | |
| Home | | 19 | 47.5 | | 26 | 44.1 |
| Rehabilitation hospital | | 7 | 17.5 | | 13 | 22.0 |
| Nursing home | | 5 | 12.5 | | 16 | 27.1 |
| Other | | 9 | 22.5 | | 4 | 6.8 |
| Control units | 52 | | | 49 | | |
| Home | | 20 | 38.5 | | 14 | 28.6 |
| Rehabilitation hospital | | 14 | 26.9 | | 18 | 36.7 |
| Nursing home | | 15 | 28.8 | | 8 | 16.3 |
| Other | | 3 | 5.8 | | 4 | 8.2 |

[a] Number of patients for whom data were available.

length of stay for hospitalized elderly patients. However, the study did not indicate that the psychiatric intervention had any effect on postdischarge placement. The findings indicating diminished psychiatric morbidity with the psychiatric intervention are still being analyzed.

During the baseline year, only 10% and 2% of the patients were referred for psychiatric consultation at Mount Sinai and Northwestern, respectively, in contrast to 79% and 61% who were evaluated by the psychiatrist during the experimental year. Patients who refused to participate constituted the bulk of those not seen. In the experimental year, approximately 50% of the elderly patients evidenced symptoms consistent with the *DSM-III-R* criteria for organic mental disorder, and many experienced delirium secondary to organic conditions that in many cases were reversible. This finding suggests that the majority of patients with organic mental disorders in the baseline year were not referred. Consequently, one mechanism for the shorter length of stay in the experimental year could have been the treatment for reversible organic mental disorders. The prevalence of organic mental disorder, and delirium in particular, is also important because of the association between delirium and death (24).

Fulop et al. (25) have demonstrated that psychiatric morbidity in the medically/surgically ill is associated with longer length of stay. Similar results were found by Levenson et al. (26). Further, Lyons et al. (27) reported that earlier psychiatric intervention was associated with earlier hospital discharge. This suggests that psychiatric screening (liaison) early in the hospitalization for medically ill patients at high risk for psychiatric morbidity is preferable to the traditional strategy of consultation referral by the primary care physician, which occurs for relatively few patients (28) and often after a major portion of the hospitalization has elapsed (27, 29). That earlier psychiatric intervention reduces length of stay has been further documented with patients who have spinal cord or head injuries (6).

The results at Northwestern Memorial Hospital also support Levitan and Kornfeld's findings, but in a somewhat complicated manner. The liaison unit, unit A, at Northwestern shared a floor with one of the control units, unit B. The second control unit, unit C, was not contiguous with unit A and was two floors away. A substantial reduction in length of stay occurred on the liaison unit. Unit B, which was contiguous and shared the same floor, discharge planner, and social worker, did not have a major change, suggesting a carry-over effect of the liaison intervention from the contiguous liaison unit, given that the length of stay in unit C, which was not contiguous to the liaison unit, increased over the two years of study. The control unit that was isolated from the liaison unit and had a completely independent staff showed a longer length of stay during the second year of the investigation.

This study indicates a cost offset from a psychiatric liaison intervention: not only could the psychiatrist's salary for performing consultations for all consenting elderly patients with hip fractures be generated from fees earned (although not in this research study), a substantial savings could accrue for the hospital. Not only was the decrease in length of stay at Mount Sinai statistically significant, but the reduction by $1,294 (per diem×2-day difference in length of stay) in hospital costs per patient ($178,572 total) has important implications for policy. The reduced length of stay with psychiatric liaison intervention at Northwestern would also have led to substantial savings ($97,361).

More than 200,000 hip fractures occur annually in the United States. One-fourth of nursing home residents fracture a hip at some time during their stays. Not only do these patients manifest substantial psychiatric morbidity while in the hospital, but such psychiatric conditions are largely undetected and these patients generally are not referred for psychiatric evaluation and treatment. Cost offset data support the position that hip fracture patients admitted to hospitals for surgical repair would benefit from psychiatric screening early in their hospital stays. The establishment of systematic psychiatric liaison on orthopedic wards for them would not only promote better patient care but accrue substantial financial savings as well.

Other studies indicate that earlier discharge of hip fracture patients prompted by reimbursement policies based on diagnosis-related groups (DRGs) may mean that these patients are less able to walk when discharged and are therefore more likely to be transferred to nursing homes after discharge and to remain there at 1 year (30). This finding indicates that the hospital's cost savings from earlier discharge are transferred to costs for other institutions in the year after surgical repair of fractured hips and that these patients have less complete restoration of function at 1 year. We are currently analyzing the 6- and 12-week follow-up data from the current study to examine this cost transfer due to earlier discharge.

Finally, this study demonstrates the advantage of multisite studies. The initial lengths of stay in the baseline year at Mount Sinai and Northwestern were significantly different. This difference indicates a need to perform psychiatric intervention studies with medically ill patients at multiple sites to overcome the idiosyncratic characteristics of a given institution and of a particular case mix. The lengths of stay in the two hospitals for patients receiving similar procedures for a homogeneous disease category (hip fracture, DRG 410) were so different to begin with that the opportunity for affecting length of stay with an intervention was less at Northwestern, where the patients stayed an average of 5 fewer days. Multisite intervention studies using identical intervention methods with homogeneous patient groups and assessment that is adequate to control for seriousness of illness and demographic variations are crucial to overcoming the pitfalls of case mix anomalies that may result from single-institution studies and heterogeneous medically ill patient groups.

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# Detection of Dissociative Disorders in Psychiatric Patients by a Screening Instrument and a Structured Diagnostic Interview

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*Objective and Method: Diagnosis and treatment of the dissociative disorders may be delayed for many years because of difficulties in detecting patients at high risk for dissociative disorders. This study investigates the utility of the Dissociative Experiences Scale (DES), a self-report instrument for dissociative experiences, in detecting patients at high risk for dissociative disorders. The clinician-administered Structured Clinical Interview for DSM-III-R Dissociative Disorders (SCID-D) was used as the diagnostic standard, and 36 outpatients with mixed diagnoses and nine normal subjects were evaluated for the presence and absence of a dissociative disorder. DES scores were then compared. Results: Results indicate that a DES cutoff score of 15–20 yields good to excellent sensitivity and specificity as a screening instrument. However, for higher cutoff points the sensitivity can be much lower. Conclusions: Thus, although the DES can be used to identify some high-risk patients, they should be further evaluated with such diagnostic instruments as the SCID-D or by in-depth clinical follow-up.*

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Difficulties in detection of the dissociative disorders may be due to 1) the intricacies of the syndromes themselves, 2) low clinician awareness, or 3) lack of systematic assessment. Several investigations have noted that a dissociative disorder may go undetected for years while the patient receives numerous misdiagnoses (1–3). Research has included the development of several instruments, including screening tools and structured interviews, for the assessment of dissociative symptoms and the dissociative disorders (4–8). A brief, self-administered instrument is needed to screen the psychiatric population for patients who are candidates for a more thorough diagnostic assessment of dissociative pathology. The Dissociative Experiences Scale (DES) is a self-report screening instrument that rates dissociative experiences and for which reliability and validity are reported (4). Median scores for the same diagnostic categories on the DES have ranged considerably in different studies (i.e., the median scores for multiple personality disorder have ranged from 40.7 [9] to 57.06 [4]). Cutoff scores for the DES for the identification of cases of dissociative disorders have not been published.

This study investigates the utility of the DES as a screening instrument for the identification of patients at high risk for dissociative disorders and assesses several possible cutoff scores. This study is similar to those performed with symptom rating scales for other psychiatric symptoms and syndromes, such as depression (10). This evaluation of the DES was carried out by using scores obtained from 45 subjects and compared with diagnoses made by using the Structured Clinical Interview for DSM-III-R Dissociative Disorders (SCID-D). The SCID-D is the first diagnostic instrument developed for the assessment of five dissociative symptom areas and for the diagnosis of the dissociative disorders, and it has proven utility in confirming known cases of dissociative disorders as well as in detecting previously unidentified cases of dissociative disorders (6, 7, 11).

## METHOD

The utility of the DES as a screening instrument was assessed by using the following components for evaluating the predictive power of diagnostic tests (12): 1)

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sensitivity: ability to correctly identify true positive cases or subjects with dissociative disorders, 2) specificity: ability to correctly identify true negative cases or subjects without a dissociative disorder, 3) false positive rate (1 minus true negatives) or the extent to which the scale incorrectly identifies those without a dissociative disorder as having one, and 4) false negative rate (1 minus true positives) or the extent to which the scale fails to detect dissociative disorders when present.

The SCID-D interview was administered and scored by the first author. All SCID-D interviews were video- or audiotaped. The video- or audiotaped interviews were scored independently by a co-rater, a psychiatric nurse who was blind to all of the patients' diagnoses by referring clinicians. After the SCID-D interview all 45 subjects completed the DES. Informed consent, including consent to video- and audiotape the interviews, was obtained from all subjects. The referring clinician's diagnosis consisted of a comprehensive assessment based on all available data, including psychological tests, past records, and observation, over a 6-month period. Comparison of diagnostic results included an evaluation of the effect of several different cutoff scores on the DES.

Forty-five subjects participated in the study. Thirty-six psychiatric patients, with a range of axis I diagnoses, as well as nine normal comparison subjects, were included. Psychiatric subjects were outpatients in active treatment at a mental health center or in private therapy. They had been in treatment with the referring physician for at least 6 months. Referring clinician diagnoses were based on *DSM-III* criteria and included schizophrenia or schizoaffective disorder (N=8), major depression (N=8), and other axis I psychiatric illnesses (including posttraumatic stress disorder and generalized anxiety disorder [N=5]), along with dissociative disorders (N=15). One patient had depersonalization disorder, six had multiple personality, and eight had dissociative disorder, not otherwise specified. Ten of the subjects had coexisting borderline personality disorder or mixed personality disorder. Psychiatric subjects were between 20 and 64 years old and had no evidence of organic brain syndrome or mental retardation. Those patients who were very agitated, gravely disabled, or at risk of suicide were excluded from the study. Most psychiatric patients (N=24) and comparison subjects (N=8) were women. Ten of the 15 patients with dissociative disorders were women, and 14 of the patients with nondissociative disorders were women. The patients and comparison subjects were of similar ages; the mean±SD ages of the patients with and without dissociative disorders and the comparison subjects were 34.3±7.7 (range=23–49), 41.2±9.9 (range=26–62), and 32.6±13.1 years (range=20–64), respectively. The normal comparison subjects volunteered following announcements at a local civic organization. Subjects from the community were excluded if they had a history of outpatient treatment for a psychiatric disorder, psychiatric hospitalization, or a suicide attempt.

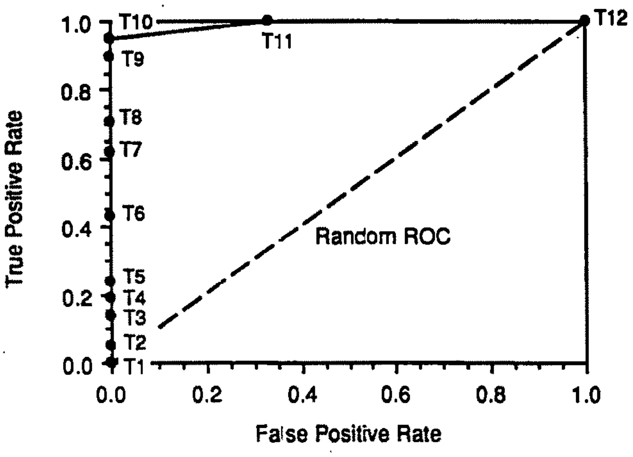
Diagnostic assessment was first made with the SCID-D (6, 7). The SCID-D investigates five groups of dissociative symptoms (amnesia, depersonalization, derealization, identity confusion, and identity alteration) and systematically rates the severity and constellation of individual symptoms as well as overall diagnosis of dissociative disorder. The SCID-D instrument is a semistructured interview and contains 200 items, including follow-up questions. The SCID-D format is modeled on the Structured Clinical Interview for DSM-III-R Disorders (13). The interviewer rates the subject as to whether or not 1) a given symptom is present and at what severity, 2) the *DSM-III-R* criteria for a dissociative disorder have been met, and 3) a past dissociative episode has occurred from which there has been recovery. (Diagnosis can be classified as present or absent.) The diagnostic information derived from the SCID-D can be viewed on a spectrum ranging from the most molar unit (a global SCID-D score [of 5 to 20]) to progressively more molecular dimensions, namely, presence of a dissociative disorder (yes, subthreshold, no), type of dissociative disorder (psychogenic amnesia, psychogenic fugue, depersonalization disorder, multiple personality disorder, and dissociative disorder not otherwise specified), and five specific dissociative symptoms (depersonalization, derealization, amnesia, identity confusion, and identity alteration) rated as absent, mild, moderate, or severe. Good to excellent reliability and discriminant validity for the SCID-D have been reported for its use both as a diagnostic instrument for the five dissociative disorders and as a tool for the evaluation of dissociative symptoms encountered within nondissociative syndromes (6). These results have been replicated in Amsterdam in a cross-national reliability and extension study of the SCID-D (11). In addition, Boon and Draijer have reported strikingly similar patterns and severity rating scores for the five dissociative symptoms in patients with dissociative disorders (11). The DES quantifies general dissociative experiences with a 28-item self-report questionnaire developed by Bernstein and Putnam (4). The questions are rated with slashes on 100-mm lines that indicate where the subject falls on a continuum for each item. The DES score ranges from 0 to 100 and represents the mean of all item scores. A high total score indicates a high level of dissociative experiences. This questionnaire has been reported to have good test-retest and split-half reliabilities. The DES is not intended to diagnose the five major dissociative disorders, but rather to screen for the presence of major dissociative psychopathology. No cutoff scores have previously been identified as indicating the presence of dissociative disorders.

## RESULTS

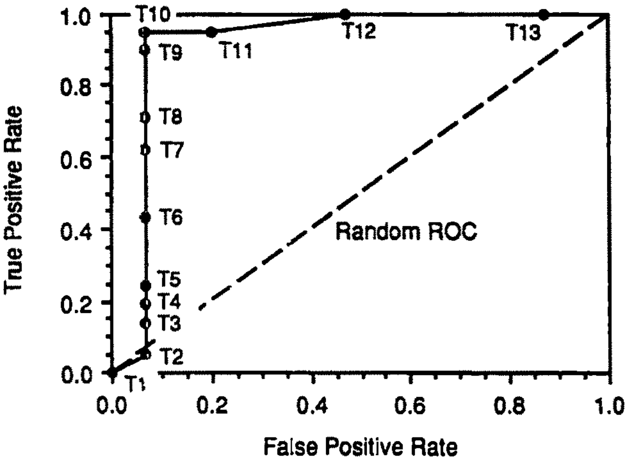
In a more general sense, several authors have recommended using signal detection methodology to evaluate the proficiency of a given screening instru-

**FIGURE 1. Receiver Operating Characteristic (ROC) Curve for the Dissociative Experiences Scale for Normal Subjects (N=9) and Psychiatric Outpatients With Mixed Diagnoses (N=36)[a]**

A. Normals as Comparison Group



B. Mixed Psychiatric Patients as Comparison Group



[a] The Structured Clinical Interview for DSM-III-R Dissociative Disorders was used as the standard. T1–T13 represent cutoff points for the Dissociative Experiences Scale.

**TABLE 1. Receiver Operating Characteristic Data on the Dissociative Experiences Scale When the Group Without Dissociative Disorders Consists of Normal Subjects (N=9)**

| Item | Value of Diagnostic Variable | False Positive Rate | True Positive Rate | True Negative Rate | Area of Trapezoid |
|---|---|---|---|---|---|
| Scale cutoff point | | | | | |
| T1 | 85 | 0.00 | 0.00 | 1.00 | 0.00 |
| T2 | 65 | 0.00 | 0.05 | 1.00 | 0.00 |
| T3 | 60 | 0.00 | 0.14 | 1.00 | 0.00 |
| T4 | 55 | 0.00 | 0.19 | 1.00 | 0.00 |
| T5 | 45 | 0.00 | 0.24 | 1.00 | 0.00 |
| T6 | 40 | 0.00 | 0.43 | 1.00 | 0.00 |
| T7 | 30 | 0.00 | 0.62 | 1.00 | 0.00 |
| T8 | 25 | 0.00 | 0.71 | 1.00 | 0.00 |
| T9 | 20 | 0.00 | 0.90 | 1.00 | 0.00 |
| T10 | 15 | 0.00 | 0.95 | 1.00 | 0.00 |
| T11 | 5 | 0.33 | 1.00 | 0.67 | 0.32 |
| T12 | 0 | 1.00 | 1.00 | 0.00 | 0.67 |
| Total | — | — | — | — | 0.99 |

**TABLE 2. Receiver Operating Characteristic Data on the Dissociative Experiences Scale When the Group Without Dissociative Disorders Consists of Psychiatric Outpatients With Mixed Diagnoses (N=36)**

| Item | Value of Diagnostic Variable | False Positive Rate | True Positive Rate | True Negative Rate | Area of Trapezoid |
|---|---|---|---|---|---|
| Scale cutoff point | | | | | |
| T1 | 85 | 0.00 | 0.00 | 1.00 | 0.00 |
| T2 | 75 | 0.07 | 0.05 | 0.93 | 0.00 |
| T3 | 60 | 0.07 | 0.14 | 0.93 | 0.00 |
| T4 | 55 | 0.07 | 0.19 | 0.93 | 0.00 |
| T5 | 50 | 0.07 | 0.24 | 0.93 | 0.00 |
| T6 | 40 | 0.07 | 0.43 | 0.93 | 0.00 |
| T7 | 30 | 0.07 | 0.62 | 0.93 | 0.00 |
| T8 | 25 | 0.07 | 0.71 | 0.93 | 0.00 |
| T9 | 20 | 0.07 | 0.90 | 0.93 | 0.00 |
| T10 | 15 | 0.07 | 0.95 | 0.93 | 0.00 |
| T11 | 10 | 0.20 | 0.95 | 0.80 | 0.12 |
| T12 | 5 | 0.47 | 1.00 | 0.53 | 0.26 |
| T13 | 0 | 0.87 | 1.00 | 0.13 | 0.40 |
| Total | — | — | — | — | 0.79 |

ment (14). The procedure involves plotting a range of sensitivity values (true positive rate, Y axis) against the corresponding false positive rate (X axis). When a screening test performs completely randomly, all values will fall along the main diagonal. On the other hand, when a screening test performs optimally, all values will fall along the left and upper boundaries, with the area under the curve summing to 1.00 or 100%. Deviations from 100% indicate the extent to which the screening test performs less than optimally.

In applying this methodology to our data, we first used normal subjects as the comparison group. For the second application, we used the psychiatric patients with mixed diagnoses as the comparison. As can be seen in figure 1, the DES performs almost optimally when the comparison group is composed of normal adults. This is confirmed by the data in table 1, which show that 99% of the area is subsumed above the main diagonal. On the other hand, the DES performs somewhat less well when the comparison group is composed of patients with mixed psychiatric diagnoses. The plot of DES cutoff points for this patient group in figure 1 shows that considerably less than 100% of the area under the curve is subsumed. This is verified by the 79% figure given in table 2. Table 1 summarizes results using 12 DES cutoff scores. Table 1 shows, at each cutoff point, the value of the DES, as well as its false positive rate, true positive rate (sensitivity), true negative rate (specificity), and the area subsumed under the curve, using the SCID-D diagnosis as the diagnostic standard for comparison and the normal subjects as the group without dissociative disorders. For normal subjects versus dissociative disorders (for DES cutoff scores ranging from ≥15 to ≥30), the range of sensitivity was 62%–95%, while specificity remained 100%. False positives remained at 0%, while false negatives (1 minus true positives) ranged between 5% and 38%. For mixed psychiatric disorders versus dissociative disorders (also for DES cutoff scores ranging from ≥15 to ≥30), the range of sensitivity was 62%–95%, while specificity remained constant at 93%. False positives remained at 7%, while false negative values ranged from 5% to 38%. For a more detailed summary of these results, see tables 1 and 2 and figure 1.

One-way analyses of variance followed by Tukey multiple range comparisons (15) showed that patients with dissociative disorders had significantly higher DES scores (mean±SD=37.15±18.24, range=7.70–82.50) than did patients with other psychiatric disorders (mean±SD=9.43±17.03, range=0–68.80) and normal comparison subjects (mean±SD=2.33±2.67, range=0–7.90) ($p<0.05$); patients with other psychiatric disorders did not differ significantly from normal comparison subjects.

Of the 15 referred patients with dissociative disorders, 14 had DES scores greater than 15, and 13 had DES scores greater than 20. Of the six patients newly identified as having a dissociative disorder on the SCID-D, all had DES scores greater than 15. This would support the ability of the DES to identify patients who are at high risk for a dissociative disorder (if a conservative cutoff score of 15 is used) and who might otherwise go undetected among psychiatric patients.

## DISCUSSION

"Symptom screening scales provide only a relatively gross screening function and should be followed by more thorough clinical evaluation" (10). However, routine clinical evaluation may be inadequate as the diagnostic standard (16), and especially in the case of the dissociative disorders, routine clinician diagnosis has resulted in cases that remain undetected for many years (1, 3). The SCID-D is a new diagnostic instrument that has good to excellent reliability and validity. The SCID-D has been previously reported as having resulted in confirmatory diagnoses of all referred cases of dissociative disorders and also has identified several new cases of dissociative disorders that have been subsequently confirmed independently by the treating clinician (6, 11).

The percentage of false negative diagnoses rises rapidly when a DES cutoff greater than 20 is used. This high percentage of false negative cases is consistent with the difficulty in evaluating dissociative symptoms by self-report, since the subject may be unaware of the symptoms. The percentage of false negative cases can be reduced by lowering the cutoff score used to identify possible cases of dissociative disorders. Considering both sensitivity and specificity, the use of a DES cutoff of 15 or 20 would seem most suitable for screening purposes, since these dividing points result in the highest sensitivity and specificity. Thus the use of a conservative cutoff of 15–20 would minimize the risk of false negative diagnoses. It should be noted that replication of these findings in other, larger samples is necessary to cross-validate these cutoff points (17), and thus the findings reported in this article should be considered preliminary. For example, previous investigators noted that "scores above 30 [on the DES] are almost always associated with DSM-III-R diagnosis of MPD" (9), but the DES alone was administered, and no information regarding the sensitivity or specificity was provided. Our study indicated that a cutoff of 30 on the DES would be too high, since this would result in a false negative rate of 38% of the dissociative disorder group. When the SCID-D is used as the standard of comparison, there is a 7% false positive rate for scores above 30 for patients with mixed psychiatric disorders, a sensitivity of 62%, and a specificity of 93%. As shown in table 2, if a cutoff score above 20 is used, the risk of false negative diagnosis is high and the sensitivity of the DES declines. As stated, a cutoff score of 15 or 20 on the DES appears to have the most acceptable sensitivity (i.e., 90%–95%).

In this study the median score on the DES for the dissociative disorder group (SCID-D diagnosis) was 33.60. A median score of 40.60 for the group with multiple personality disorder compares to 40.7 found by Ross et al. (9) and 57.06 found by Bernstein and Putnam (4). Possible explanations for the lower median scores for the dissociative disorder group and the group with multiple personality disorder in the present study than in the study by Bernstein and Putnam include 1) the ability of the SCID-D to diagnose patients with multiple personality disorder who may present with subtler symptoms and lower DES scores and 2) the ability of the SCID-D to identify patients with other dissociative disorders, such as depersonalization disorder and dissociative disorder not otherwise specified, who have less dissociative pathology than patients with multiple personality disorder.

Dissociative symptoms are nonspecific and can be seen in patients with a wide variety of dissociative and other psychiatric disorders (18). The results of the present study indicate that with appropriate cutoffs (i.e., ≥15–20), the DES can be used successfully to screen for cases of dissociative disorders, particularly multiple personality disorder. However, it requires the use of a confirmatory instrument such as the SCID-D in order to diagnose definitively the presence of a dissociative disorder and to identify the specific disorder and symptom severity. Most importantly, one needs to evaluate the wide variation in median DES scores for the multiple personality disorder groups as well as the wide range of DES scores for the groups with mixed psychiatric diagnoses (in our and other studies). Such variation would preclude the suggestion of exact DES cutoff scores to separate subjects with dissociative disorders from other subjects.

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# A Review of 32 Cases of Tardive Dystonia

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*Objective: Tardive dystonia, historically combined with tardive dyskinesia, is now viewed as probably having a different pathophysiology, course, outcome, and treatment response than tardive dyskinesia. In addition, patients with tardive dystonia are reported to be younger, and most are men. This study evaluates characteristics of 32 patients with tardive dystonia and compares results to other reports. Method: Twenty-four patients had been referred for research purposes and were videotaped, while eight had been followed clinically. Two of the authors reviewed all available videotapes and clinical reports to assess the course of symptoms over time. For global ratings and ratings of affected body parts, two scales were used: the Abnormal Involuntary Movement Scale (AIMS) for tardive dyskinesia and a similar scale for tardive dystonia. The method of case finding does not provide incidence or prevalence data for tardive dystonia. Results: Fifty-nine percent of the patients experienced onset of tardive dystonia symptoms within 6 years of antipsychotic drug exposure; women had a shorter exposure time. No patient had complete remission of tardive dystonia symptoms, and 22 were moderately or severely impaired when their movements were most prominent. Conclusions: While epidemiological studies of tardive dystonia have yet to be performed, these results support the observations of others that most patients with tardive dystonia are men, have a short history of exposure to antipsychotic drugs, and may initially present with blepharospasm. Tardive dystonia rarely remits completely, can cause notable disability, and may partially respond to anticholinergic agents.*

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Tardive dystonia is a disorder of abnormally sustained posturing associated with the use of dopamine-receptor blocking agents such as antipsychotic drugs. Although chronic dystonia was first recognized in the 1960s, patients with tardive dystonia were combined with those who had tardive dyskinesia, with all abnormal movements rated compositely on the Abnormal Involuntary Movement Scale (AIMS) (1). Several reports suggest that tardive dystonia generally affects a different population of psychiatric patients and might have a different pathophysiology, course, outcome, and treatment response than tardive dyskinesia (2–5). This paper adds to the growing literature on tardive dystonia by presenting data on 32 systematically assessed patients.

## METHOD

We identified 32 patients with tardive dystonia who were followed at two major hospitals. The majority of the patients (N=24) were referred for research purposes and were videotaped as part of research protocols. The remaining eight were selected from hospital records as patients with clear descriptive histories of tardive dystonia. These patients were not videotaped. Our selection criteria do not provide incidence or prevalence data for this disorder; these patients do not represent all cases of tardive dystonia seen at these institutions but only those for whom videotapes or clear clinical descriptions to make a diagnosis of tardive dystonia were available. In all cases, time of onset of the movement disorder was determined by medical history or record review.

Diagnosis of tardive dystonia was confirmed by a neurologist who used the four essential criteria established by Burke et al. (2): 1) the presence of dystonic movements or postures, 2) development during treatment with neuroleptics or within 2 months of drug cessation, 3) exclusion of other causes of secondary dystonia by clinical and laboratory evaluation, and 4) no family history of dystonic movement disorder. The

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**TABLE 1. Characteristics of 32 Patients With Tardive Dystonia**

| Item | N | % | Mean | SD | Median | Range |
|---|---|---|---|---|---|---|
| Diagnosis | | | | | | |
| Schizoaffective or mood disorder | 22 | 69 | | | | |
| Schizophrenia | 8 | 25 | | | | |
| Other | 2 | 6 | | | | |
| Age at onset (years) | | | 36 | 13 | 32 | 22–69 |
| Men (N=21) | | | 34 | 12 | 30 | |
| Women (N=11) | | | 40 | 15 | 36 | |
| Duration of antipsychotic drug use before onset (years)[a] | | | 6.3 | 5.6 | 5.0 | 0.3–24.0 |
| Men (N=20) | | | 6.8 | 5.5 | 6.0 | |
| Women (N=10) | | | 5.5 | 5.8 | 2.3 | |

[a] N=30.

dystonias were classified into three subtypes: 1) focal (one body part), 2) segmental (two to four body parts), and 3) generalized (involvement of face, neck, trunk, at least one upper extremity, and at least one lower extremity) (2).

To assess type of symptom and severity, initial videotapes were reviewed for 24 patients and charts reviewed for eight. A global severity score was determined and agreed upon by two raters. We were able to assess global severity over time in 29 patients. Twelve patients were reevaluated in person; the last visit, or videotaped visit, was used for 17 patients; three patients were not included in the change data because of inadequate information. For 19 patients we could assess changes in severity both globally and for individual body parts by using the AIMS for choreoathetosis and our own rating scale of tardive dystonia, which contained the following items: facial grimacing, blepharospasm, torticollis, retrocollis, antecollis, axial torsion dystonia, and opisthotonos. Ratings of upper limbs and lower limbs were divided into inversion, eversion, extension, and flexion. Like the AIMS, movements were rated individually on a 5-point scale, and there was one global severity item.

## RESULTS

Of the 32 patients diagnosed with tardive dystonia, a majority were men and had a diagnosis of schizoaffective or mood disorder (table 1). Overall, age at onset of tardive dystonia ranged from 22 to 69 years (median=32). The most frequently prescribed antipsychotic medications were trifluoperazine (N=18), chlorpromazine (N=16), and haloperidol (N=11). The duration of antipsychotic drug use before the onset of tardive dystonia ranged from 0.3 to 24 years (N=30). Despite this large range, the majority (59%, N=19) of patients had taken antipsychotic drugs for less than 6 years, and only six patients (19%) had received these drugs for longer than 10 years. Women had a shorter exposure time than men (median=2.3 versus 6 years) before symptom onset.

When abnormal movements first developed, 25 patients (78%) had tardive dystonia alone, two (6%) had tardive dyskinesia alone, and there were inadequate descriptive data for five (16%). Dystonia was focal in 18 patients (56%, 11 men and seven women), with the face involved in 11, the neck in six, and an arm in one patient. For seven patients, increased blinking or blepharospasm was the first symptom noted. Segmental movements occurred in seven patients (22%, four men and three women). For the remaining seven patients (22%), clear descriptions of onset of movements were not available.

The length of time from onset of tardive dystonia to first evaluation was 2.4 years. The mean±SD time from first evaluation until last evaluation was 4.9±3.3 years (range=1–10); the overall duration of tardive dystonia was 1–14 years. As noted earlier, three patients (two with focal and one with segmental tardive dystonia) were excluded from follow-up data because of insufficient clinical information.

At the last evaluation, 11 of the 17 patients with focal dystonia who had follow-up examinations had converted to segmental dystonia, leaving only six (21%, four men and two women) with focal symptoms. All patients with focal dystonia had neck or face involvement.

A total of 22 patients (76%, 15 men and seven women) had segmental dystonia at last evaluation. The neck was the most frequently involved body part (N=21), and 11 patients had two concurrent neck movements (e.g., torticollis and retrocollis). Eighteen (82%) of the patients with segmental dystonia had facial movements, including 10 with blepharospasm and 14 with grimacing. Twelve patients had two or more facial movements.

Trunkal movements were found in 11 patients with segmental dystonia, while nine had upper and three lower extremity involvement. Of the patients with segmental dystonia, 10 had involvement of two body parts, seven of three body parts , and five of four body parts. One patient had generalized tardive dystonia. Initial and last ratings of tardive dyskinesia and tardive dystonia for individual patients are provided in table 2, which also summarizes clinical impression of change for each patient.

Twenty-seven patients (84%) had both tardive dyskinesia and tardive dystonia sometime during the course of their movement disorder history. Only five (16%) had tardive dystonia alone. At last evaluation, 10 patients no longer had symptoms of tardive dyskinesia, but none of the patients with tardive dystonia had fully recovered. In addition, two patients developed tardive myoclonus, eight parkinsonism, and one stereotypies.

No one had a complete remission of tardive dystonia symptoms. Fifteen (52%) of the patients had improvement of tardive dystonia movements at last evaluation, while 14 (48%) were unchanged or worse. For the improved group, seven were no longer taking antipsy-

TABLE 2. Ratings of 32 Patients With Tardive Dystonia

| Patient | Sex | Age at Onset (years) | Psychiatric Diagnosis | Duration of Tardive Dystonia (years) | Global Abnormal Involuntary Movement Scale Score | | Global Tardive Dystonia Scale Score | | Clinical Impression of Change[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | First | Last | First | Last | |
| 1 | M | 22 | Schizophrenia | 4 | 3 | 2 | 3 | 3 | Worse |
| 2 | M | 22 | Mood disorder | 8 | 0 | 0 | 3 | 2 | Better |
| 3 | F | 22 | Schizophrenia | 5 | 0 | 2 | 2 | 2 | Better |
| 4 | M | 24 | Schizoaffective disorder | 6 | 3 | 0 | 2 | 3 | Worse |
| 5 | F | 24 | Mood disorder | 5 | 0 | 0 | 3 | 3 | Same |
| 6 | M | 25 | Schizophrenia | 9 | 2 | 2 | 2 | 2 | Better |
| 7 | M | 26 | Mood disorder | — | 2 | — | 3 | — | — |
| 8 | M | 26 | Schizophrenia, obsessive-compulsive disorder | 10 | 0 | 0 | 2 | 3 | Worse |
| 9 | M | 26 | Mood disorder, obsessive-compulsive disorder | 14 | 2 | 2 | 4 | 4 | Better |
| 10 | M | 27 | Mood disorder | 12 | 3 | 2 | 3 | 2 | Better |
| 11 | M | 27 | Mood disorder | 12 | 2 | 0 | 3 | 2 | Better |
| 12 | F | 27 | Mood disorder | 3 | 1 | 0 | 3 | 3 | Same |
| 13 | M | 28 | Schizophrenia | 6 | 3 | 2 | 3 | 4 | Same |
| 14 | M | 30 | Schizophrenia | 1 | 2 | 0 | 3 | 3 | Same |
| 15 | M | 31 | Mood disorder | 12 | 2 | 3 | 3 | 3 | Worse |
| 16 | F | 32 | Mood disorder | 4 | 3 | 2 | 3 | 1 | Better |
| 17 | M | 32 | Mood disorder | 2 | 2 | 2 | 2 | 3 | Same |
| 18 | M | 32 | Schizophrenia | 6 | 0 | 0 | 3 | 2 | Better |
| 19 | F | 33 | Mood disorder | 6 | 0 | 0 | 4 | 3 | Better |
| 20 | F | 36 | Mood disorder | 6 | 4 | 2 | 4 | 4 | Worse |
| 21 | M | 38 | Schizoaffective disorder | 6 | 3 | 2 | 3 | 3 | Better |
| 22 | F | 40 | Mood disorder | 10 | 3 | 4 | 3 | 4 | Worse |
| 23 | M | 43 | Mood disorder | 8 | 3 | 2 | 3 | 1 | Better |
| 24 | M | 43 | Schizophrenia | 11 | 3 | 3 | 4 | 4 | Worse |
| 25 | M | 44 | Psychosis | 10 | 3 | 3 | 3 | 3 | Same |
| 26 | F | 44 | Mood disorder | 3 | 3 | 3 | 4 | 2 | Better |
| 27 | F | 45 | Mood disorder | 4 | 3 | — | 4 | — | — |
| 28 | M | 49 | Mood disorder | 14 | 3 | 0 | 3 | 1 | Better |
| 29 | M | 58 | Toxic psychosis | 3 | 3 | 3 | 4 | 3 | Better |
| 30 | F | 64 | Mood disorder | — | 2 | — | 3 | — | — |
| 31 | M | 68 | Mood disorder | 12 | 2 | 3 | 3 | 4 | Worse |
| 32 | F | 69 | Anxiety disorder | 8 | 2 | 1 | 3 | 2 | Better |

[a] Change in tardive dyskinesia and tardive dystonia. Rating based on overall clinical impression and not the global scores alone.

TABLE 3. Medications Taken at First and Last Evaluations by 32 Patients With Tardive Dystonia

| Medication | Number of Patients | |
|---|---|---|
| | First Evaluation | Last Evaluation |
| Antipsychotics | 25 | 16 |
| Benzodiazepines | 12 | 25 |
| Lithium | 7 | 12 |
| Anticholinergics | 5 | 8 |
| Antidepressants | 4 | 9 |
| Antihistamines | 3 | 4 |
| β-blockers | 1 | 2 |
| Anticonvulsants | 0 | 3 |
| Baclofen | 0 | 2 |
| Lecithin | 0 | 1 |

TABLE 4. Effect of Medications Administered After the Development of Tardive Dystonia in 32 Patients

| Medication | Definitely Improved | Possibly Improved | Unimproved or Worse |
|---|---|---|---|
| Anticholinergics[a] | 6 | 7 | 10 |
| Cholinergics | 2 | 4 | 10 |
| Benzodiazepines | 12 | 4 | 7 |
| Reserpine | 1 | 2 | 2 |
| Diphenhydramine | 1 | 3 | 1 |
| Lithium | 1 | 1 | 4 |
| Haloperidol | 2 | 0 | 2 |
| Carbamazepine | 1 | 0 | 0 |
| Propranolol | 0 | 3 | 2 |
| Clozapine | 1 | 0 | 0 |
| Baclofen | 2 | 1 | 2 |
| Neural growth factor | 0 | 0 | 1 |

[a] Amitriptyline, benztropine, trihexyphenidyl.

chotic medication, four were taking higher doses, three were taking lower doses, and medication dose was unknown for one. For the unchanged or worse group, four were no longer taking antipsychotic drugs, four were taking higher doses, one was taking a lower dose, three remained at the same dose, and the dose was unknown for two. Thirteen (87%) of the improved patients (N=15) did have shorter exposure to antipsychotic drugs (less than 6 years) before onset of tardive dystonia. For the unchanged or worse group (N=14),

**TABLE 5. Clinical Reports of Tardive Dystonia**

| Item | N | Sex | Mean Age at Onset (years) | Diagnosis | Number of Patients in Clinical Remission |
|---|---|---|---|---|---|
| Kang et al. (5) | 67 | 35 M<br>32 F | 34<br>44 | 22 Schizophrenia<br>28 Mood disorder<br>8 Anxiety disorder<br>7 Other (aggressive, multiple somatic complaints, chronic gastrointestinal complaints)<br>2 Unspecified | 5 |
| Yassa et al. (6) | 7 | 5 M<br>2 F | 35<br>61 | 5 Schizophrenia<br>1 Mental retardation<br>1 Senile dementia | 0 |
| Yassa et al. (7) | 8 | 6 M<br>2 F | 46.8[a] | 5 Schizophrenia<br>3 Organic mental disorder | — |
| Gardos et al. (8) | 10 | 6 M<br>4 F | 34<br>32 | 4 Schizophrenia<br>5 Mood disorder<br>1 Obsessive-compulsive disorder | 0 |
| Gimenez-Roldan et al. (9) | 9 | 5 M<br>4 F | 34<br>38 | 6 Schizophrenia<br>2 Chronic psychosis<br>1 Schizoaffective disorder | 0 |
| Lieberman et al. (10) | 5 | 4 M<br>1 F | 28<br>29 | 3 Schizophrenia<br>2 Mood disorder | 0 |
| Lieberman et al. (11) | 5 | 5 M | 32 | 2 Schizophrenia<br>3 Mood disorder | — |
| Yassa et al. (12) | 9 | 7 M<br>2 F | 44.1[a] | — | — |
| Yadalam et al. (13) | 4 | 3 M<br>1 F | 26<br>38 | 2 Schizophrenia<br>2 Mood disorder | 1[b] |
| Wojcik (present study) | 32 | 21 M<br>11 F | 34<br>40 | 8 Schizophrenia<br>2 Schizoaffective disorder<br>20 Mood disorder<br>2 Other | 0 |
| Total | 156 | 97 M<br>59 F | 33 M[c]<br>44 F[c] | | 6 |

[a] Group mean.
[b] After thalamotomy.
[c] Excluding data from Yassa et al. (7, 12).

nine (64%) had more than 6 years' exposure to antipsychotic drugs.

Table 3 shows the number of patients taking medications (broken down by class), both when they were first seen and at their last evaluation. The medications taken at last evaluation might be viewed as those which controlled tardive dystonia best or at least did not appear to worsen it. Benzodiazepines were most frequently prescribed (N=25), followed by antipsychotic drugs (N=16) and lithium (N=12). To treat tardive dystonia, a variety of medications were tried, but no clearcut response to any single class of drug was evident (table 4).

Twenty-two patients (69%) were moderately or severely disabled when their movement disorder was most prominent. Impairments of speech, vision, sitting, and walking occurred, which interfered with activities of daily living and were socially embarrassing. Patients often found these movements to be painful; five patients had fixed abnormal postures due to atrophy. Eight patients (25%) reported mild interference with functioning; only two patients had no complaints of disability. Ten disabled patients stopped their antipsychotic medication; six improved, one was unchanged, and three worsened.

Nineteen of the 24 patients' first evaluation videotapes were rerated with the AIMS and the tardive dystonia rating scale. Their scores were compared to either their last evaluation or last videotape (mean duration=53±38 months). For these 19 patients, there was minimal improvement in the AIMS score over time (from a mean score of 5.6±4.8 to 4.7±4.0) and minimal change in the tardive dystonia rating score (from a mean score of 7.0±4.2 to 6.1±4.6).

## DISCUSSION

This paper describes 32 patients diagnosed with tardive dystonia, considered a subtype or an atypical form of tardive dyskinesia (3, 4). When we add our patients to previous reports (5–13), there are now 156 well-described cases of tardive dystonia: 97 men and 59 women (table 5). Men tend to be younger than women. A majority of our patients have mood disorders, while in other series 40% are schizophrenic, 45% have mood disorders, and the remaining 15% have a variety of diagnoses including anxiety disorders, organic brain syndromes, and gastrointestinal disorders.

While most tardive dyskinesia patients are older (90% are over the age of 40) (4), in tardive dystonia the opposite is found: 63% (N=87 of 139) are under age 50. Casey (4) suggests that the incidence of tardive dyskinesia might vary with age at first exposure; younger patients may have a linear curve, with a 3%–4% new case incidence each year, while the elderly (over age 60 years) show a sigmoid dose response curve with large risk (50%) occurring in the first 3 years of drug treatment. To date, similar epidemiological studies of tardive dystonia have not been performed, so that its incidence rate and risk groups are still to be defined. However, it does seem that tardive dystonia patients, especially the young, do have a short exposure history (14).

While withdrawal dyskinesias are common, withdrawal dystonia appears to be uncommon and remission rare (14). Only six were considered to have achieved complete remission, one of those after a thalamotomy. Furthermore, unlike tardive dyskinesia, tardive dystonia frequently causes pain and disability.

Blepharospasm, repeated contractions of the orbicularis oculi muscle, may range from increased blink rate to prolonged eye closure. Blepharospasm can be idiopathic or caused by neurological disorders such as encephalitis or seizures (15, 16), but it is often associated with neuroleptic drug use. Some authors have considered it a sign of tardive dyskinesia, but, due to its dystonic nature, we suggest that it is more appropriately grouped with dystonia. Both the present study and that of Gardos et al. (8) noted an increase in blink rate as a common early symptom of tardive movement disorders. If a patient with blepharospasm is psychiatrically stable, it may be advisable to taper neuroleptic dose and look for emerging movements.

A related disorder, tardive myoclonus (17), with brief, involuntary muscle contractions and jerking movements, has been described. Two of our patients developed tardive myoclonus in addition to tardive dystonia. It is unclear if the recent increase in reports of other tardive movements is the result of increased recognition, more careful examination, or other as yet unknown factors.

The responses of tardive dyskinesia and tardive dystonia to treatment have similarities and differences. Both types of movement disorder improve, at least temporarily, with dopamine blocking and dopamine depleting agents. Kang et al. (5) found tetrabenazine most helpful for tardive dystonia, while Lieberman's group (10, 11) reported bromocriptine beneficial within a therapeutic window. Both groups of investigators observed that anticholinergic agents, which usually temporarily aggravate or uncover tardive dyskinesia (8, 12), provided some benefit for tardive dystonia. Our findings support the contention that at least some patients with tardive dystonia are benefited by anticholinergic agents (10). Given the persistent and potentially disabling nature of tardive dystonia, neuroleptics should be judiciously prescribed. Although indicated at times in the treatment of mood disorders, neuroleptic use should be avoided, if at all possible, with this diagnostic group.

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# Comparison of the Effects of Hydrochlorothiazide and Furosemide on Lithium Disposition

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*Objective: This study examined the interaction between lithium and diuretics, comparing both the pharmacokinetic and the pharmacodynamic variables of hydrochlorothiazide, furosemide, and placebo. Method: The study, which took place in an outpatient research clinic of a university hospital, used a double-blind, placebo-controlled crossover design. The subjects were normal, healthy male volunteers who responded to recruitment announcements. Thirteen subjects entered and completed the study. All subjects took lithium, 300 mg b.i.d., for 6 weeks. Hydrochlorothiazide, 25 mg b.i.d.; furosemide, 20 mg b.i.d.; and placebo were given during weeks 2, 4, and 6 in a random order of assignment. Serum lithium levels and indices of diuretic activity were measured during each week. Results: The subjects' serum lithium levels after 5 days of taking hydrochlorothiazide were significantly higher than after 5 days of taking furosemide and placebo. At the doses studied, hydrochlorothiazide was also more potent than furosemide in increasing plasma renin activity, increasing sodium excretion, and decreasing lithium excretion. Conclusions: The observed differences between diuretics in effects on serum lithium may have been due to differences in the potency of the diuretics at the doses studied as well as in the site of action of the diuretic effect. The results must be interpreted cautiously, however, because the effects were small and of questionable clinical significance, and the study used healthy volunteers and low doses of lithium instead of psychiatric patients and the usual therapeutic levels of lithium.*

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Interaction between lithium and other drugs, leading to increased serum lithium levels, is a common and clinically significant concern. It is widely accepted that sodium-depleting diuretics increase lithium retention (1–3). If a diuretic is initiated after a steady-state lithium serum concentration is achieved, a decrease in the dose of lithium is often required to prevent toxicity (4). The pharmacokinetic interaction between lithium and diuretics has been documented primarily with thiazide diuretics (3); interaction with other classes of diuretics has been less studied.

Reabsorption of lithium in the renal tubules is similar to that of sodium, except that lithium is not significantly reabsorbed at the distal tubule (5). Since reabsorption of sodium and lithium at proximal sites is competitive, blockade of sodium transport at the distal tubule without alteration of lithium transport leads to increased lithium reabsorption. Blockade of sodium reabsorption at a more proximal site where both ions are reabsorbed, such as the ascending limb of Henle's loop, might be expected to maintain the sodium-lithium balance better and be less likely to increase serum lithium.

Furosemide, a loop diuretic, was suggested as the cause of lithium retention in two instances (6, 7), but confounding factors such as sodium-restricted diets, electrolyte and fluid imbalance, and dehydration prevented a conclusive assessment. Two small open-label studies have considered the lithium-furosemide combination. Jefferson and Kalin (8) gave furosemide, 40 mg/day, then hydrochlorothiazide, 50 mg/day, to five normal volunteers who had been stabilized on a regimen of lithium carbonate, 300 mg t.i.d. Treatment with hydrochlorothiazide resulted in increased serum lithium levels, whereas furosemide caused no significant change. Saffer and Coppen (9) gave varying doses of furosemide once daily to six elderly outpatients with elevated blood pressure who had been stabilized on a lithium regimen and found that furosemide had no ef-

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fect on serum lithium levels. In both studies, the lack of effect of furosemide on serum lithium levels was attributed to furosemide's different site of diuretic action in the renal tubule as compared to that of thiazide agents; however, indices of diuretic potency were not studied.

Use of a diuretic that does not increase serum lithium levels would greatly simplify treatment when the combination is indicated and would also decrease the risk to patients. Since previous work has used small samples under nonblind conditions, further study documenting the effects of different classes of diuretics on serum lithium levels is needed. Additionally, the pharmacodynamics of the lithium-diuretic interaction have not been examined. While differences in site or sites of action are clearly a possible explanation for different effects of diuretics on lithium levels, it is also possible that the clinical potencies of hydrochlorothiazide and furosemide at commonly used doses are not equivalent. For these reasons, we undertook a reexamination of the lithium-diuretic interaction, comparing hydrochlorothiazide, furosemide, and placebo and considering both the pharmacokinetic and the pharmacodynamic variables.

## METHOD

The comparative effects of furosemide and hydrochlorothiazide on serum lithium levels were assessed in this study by a placebo-controlled, random-assignment, double-blind crossover design. Subjects were recruited through announcements posted in an academic medical center and in the local newspaper. They were required to be free of all drugs, including ethanol, caffeine, and tobacco, for 1 week before enrollment and during the study and to have no history or family history of psychiatric illness. Screening visits included physical and laboratory examinations. Thirteen normal, healthy male volunteers whose ages ranged from 22.7 to 36.3 years (mean±SD=29.9±4.1 years) were chosen to be the subjects. Informed consent was obtained from all subjects after the study procedures had been fully explained.

The subjects received lithium, 300 mg every 12 hours, for 6 weeks. The test drugs (identical-appearing capsules of hydrochlorothiazide, 25 mg; furosemide, 20 mg; or placebo) were given every 12 hours during weeks 2, 4, and 6. Assignment to the order of test-drug administration was done according to a random permuted blocks scheme. Week 1 served as a stabilization phase, and weeks 3 and 5 served as test-drug washout phases. Subjects were instructed to maintain as consistent a diet and fluid intake as possible throughout the study.

Blood was collected on the morning after the fifth day of each week, before the first daily dose of medication. This was done to ensure that at least five drug half-lives had passed and that the subjects had steady-state serum lithium concentrations (1). A 24-hour urine collection was required at the end of each week. Quantitative analysis of lithium in serum and urine was performed by atomic absorption spectrophotometry (10). Additional variables measured weekly to evaluate diuretic effects included weight, blood pressure, heart rate (after the subject had been supine for 3 minutes and immediately upon standing), plasma renin activity (after the subject had been recumbent for 30 minutes), serum sodium and creatinine levels, urine sodium and creatinine levels, and urine volume. Fractional excretion ratios of sodium and lithium were calculated. Mood changes possibly caused by lithium were monitored with the Zung Self-Rating Depression Scale (11).

Statistical analysis of group means was performed with an analysis of variance (ANOVA) for subjects and treatments. A Scheffé post hoc analysis was used to compare treatment means when the treatment source in the ANOVA was significant at the a priori level of p<0.05.

**TABLE 1. Serum Lithium Levels of 13 Healthy Volunteers Given Lithium and Sequential Trials of Hydrochlorothiazide, Furosemide, and Placebo**

| | Lithium Level (meq/liter) | | | |
|---|---|---|---|---|
| | Baseline | | Day 5[a] | |
| Condition | Mean | SD | Mean | SD |
| Hydrochlorothiazide | 0.30 | 0.10 | 0.37 | 0.09 |
| Furosemide | 0.29 | 0.06 | 0.29 | 0.07 |
| Placebo | 0.26 | 0.07 | 0.28 | 0.07 |

[a] Significant difference between hydrochlorothiazide condition and furosemide and placebo conditions after 5 days of treatment (F=9.19, df=1, 24, p<0.001).

## RESULTS

All 13 subjects enrolled in the study completed the 6-week trial. Their mean serum lithium levels during the study are shown in table 1. The Drug by Time interaction was significant, and no differences were observed within the baseline period. Serum lithium levels after 5 days of concurrent treatment with hydrochlorothiazide were significantly higher than those after 5 days of furosemide or placebo.

There were no significant differences among test groups in effects on weight, vital signs, and urine volume. Some differences were noted in laboratory indicators of diuretic activity. Hydrochlorothiazide had a significantly greater effect than furosemide and placebo on increasing plasma renin activity (hydrochlorothiazide, 9.1 ng/ml per hour; furosemide, 3.2 ng/ml per hour; placebo, 1.9 ng/ml per hour; F=34.42, df=1, 24, p<0.0001), on increasing sodium excretion (hydrochlorothiazide, 28.6%; furosemide, –0.25%; placebo, 0%; F=7.65, df=1, 24, p<0.003), and on decreasing lithium excretion (hydrochlorothiazide, 27.0%; furosemide, –19.0%; placebo, 5.6%; F=12.20, df=1, 24, p<0.002). Interestingly, furosemide differed from placebo on none of the diuretic parameters and was actually associated with a slight overall decrease in sodium excretion, although variance was large and there were both positive and negative individual values (range=–40.8% to +32.4%).

## DISCUSSION

The results of this blind, placebo-controlled crossover study support the findings of previous open studies (8, 9) which showed that hydrochlorothiazide, but not furosemide, increases serum lithium levels. The absolute changes in serum lithium levels after hydrochlorothiazide treatment were small (mean±SD=0.07±0.02 meq/liter), although the changes reflect an increase of 23.3%, consistent with the previous literature (12, 13). Serum lithium levels achieved while the subjects were taking hydrochlorothiazide were well below those generally considered therapeutic in the treatment of bipolar disorder (0.60–1.40 meq/liter). A lithium dose of 300 mg b.i.d. was selected so that even if the diuretics dramatically increased serum levels, study subjects would be unlikely to experience toxicity.

The clinical significance of the observed size of the diuretic effect, even on a percentage basis, is questionable when extrapolated to lithium serum levels well within the usual therapeutic range. There are several possible explanations for the apparent discrepancy between these results and the belief that thiazide diuretics can increase serum lithium to potentially toxic levels. Indeed, Himmelhoch et al. (4) demonstrated dose-dependent effects of chlorothiazide ranging up to a 68% reduction in lithium clearance.

First, the subjects in the study were normal, healthy volunteers with no personal or family history of psychiatric illness or hypertension. It is possible that the dynamics of lithium and diuretic effects and disposition are different in such individuals than in patients with psychiatric or cardiovascular disorders. Neither hydrochlorothiazide nor furosemide demonstrated a significant fluid diuresis relative to placebo.

Second, the doses of lithium and diuretics were low relative to those used in clinical practice. Although 50 mg/day of hydrochlorothiazide and 40 mg/day of furosemide are commonly used clinical doses, much larger doses of both drugs are also commonly used. The effect of diuretics on serum lithium levels may not necessarily be linear, and the effects of diuretics on very low serum lithium levels may not be the same as on levels within the usual therapeutic range.

Third, in a crossover study design there is a risk of residual effects between treatments. We controlled for residual effects by using a 1-week washout period between diuretic phases and by measuring serum lithium levels twice at the end of each study phase to verify serum steady-state levels. Since the elimination half-life of lithium is known to average 20–24 hours, a 5-day washout period would allow at least five half-lives in healthy subjects (1).

At the dose used in this study (20 mg b.i.d.), furosemide had essentially no effect on serum lithium levels. It is possible that when combined lithium-diuretic therapy is indicated, furosemide would be a safer and simpler alternative to a thiazide diuretic at these doses unless other factors indicate the choice of a thiazide. Indeed, a downward adjustment of lithium dose concurrent with the addition of furosemide could lead to a drop in serum lithium levels and potential loss of therapeutic efficacy. Maintaining the pre-furosemide lithium regimen while continuing to monitor serum lithium levels appears to be a better approach according to our data.

The pharmacodynamic explanation for the different effects on serum lithium levels that we observed with hydrochlorothiazide and furosemide is inconclusive. Previous reports have suggested that the difference in the site of action is the explanation for differences in the effects of the two diuretics on lithium levels (8, 9). The saluretic effect of thiazide diuretics is mediated almost exclusively at the distal tubule, where lithium reabsorption is insignificant. Furosemide works primarily at the ascending limb of Henle's loop and could be expected to affect both sodium and lithium transport if the tubular membrane cannot differentiate between the two ions at that site.

Another possible factor is pharmacokinetic differences between the diuretics. Furosemide is known to be significantly shorter acting than hydrochlorothiazide (14). When given on a once-daily basis, it is theoretically possible that furosemide only transiently affects serum lithium levels and that reequilibration occurs within 24 hours. In an attempt to control for this possibility, we divided the doses of both diuretics and administered them every 12 hours (hydrochlorothiazide, 25 mg b.i.d., and furosemide, 20 mg b.i.d.).

The effects of hydrochlorothiazide and furosemide on indices of diuretic activity were equivalent on most of the variables studied. Indeed, hydrochlorothiazide, furosemide, and placebo all showed no significant difference in effects on weight, blood pressure, heart rate, serum sodium and creatinine levels, and urine volume. Hydrochlorothiazide was, however, significantly more potent than furosemide and placebo in increasing plasma renin activity, increasing sodium excretion, and decreasing lithium excretion.

Our data indicate that the difference in the site of diuretic action may not be the sole factor in explaining the difference in effect on serum lithium levels. At the doses used in this study, there are differences between the two drugs in certain indices of diuretic potency. A greater effect of one over the other in enhancing sodium excretion, in particular, raises the possibility that lithium retention may be differentially affected as a result. It is well-known that sodium depletion causes lithium retention. Higher doses of hydrochlorothiazide and furosemide could potentially have effects different from those observed in this study.

Our study also raises questions about differential effects and mechanisms of other drugs that affect electrolyte transport. Amiloride has been shown in two studies to cause no significant effect on serum lithium levels when used in the treatment of lithium-induced polyuria (15, 16). Enalapril and other angiotensin converting enzyme inhibitors have been reported to cause lithium retention resulting in toxicity (17, 18). Additional study of the nature of the interaction between lithium and drugs that affect renal function is needed to clarify which drugs can be most safely combined with lithium.

In summation, this study showed that furosemide at a dose of 40 mg/day does not significantly affect serum lithium levels in physically healthy individuals. Thus, it may be a safer and simpler approach to combining lithium and a diuretic than using hydrochlorothiazide at 50 mg/day. When lithium and furosemide are combined, patients should be at a lesser risk of experiencing toxicity. There should be no need for adjustments of lithium doses in already stabilized patients. Continued close monitoring of serum lithium levels is always indicated. Our results must be interpreted cautiously, however, because of the subjects we used and the doses of lithium and diuretics we gave. Additional information collected from a study of psychiatric patients in which other drug doses are used would be helpful.

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# Fluoxetine in the Treatment of Borderline and Schizotypal Personality Disorders

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*Twenty-two patients meeting the criteria for borderline or schizotypal personality disorder or both participated in a prospective, nonblind 12-week trial of fluoxetine. There were significant reductions in self-injury and in scores on the Hopkins Symptom Checklist regardless of diagnosis. The results suggest that controlled trials of fluoxetine and investigations of the serotonergic system in these disorders would be useful.*

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Borderline and schizotypal personality disorders are possibly related clinical entities. These two disorders frequently coexist (1), have high levels of morbidity and mortality, and are fairly common (2).

Similarities also exist between both borderline and schizotypal personality disorders and obsessive-compulsive disorder. All three disorders are frequently accompanied by generalized anxiety, panic attacks, depression, body dysmorphias (including bulimia and anorexia), dissociative disorders, affective lability, suicidality, hostility, and obsessive-compulsive traits (2, 3).

Several studies (4–6) have suggested that some of these symptoms (e.g., depression, affective lability, suicidality, hostility, and obsessive-compulsive traits) could be due to serotonergic dysfunction. There is considerable evidence for serotonergic abnormality in obsessive-compulsive disorder, and serotonergic agents are efficacious in treating the disorder (5). Carbamazepine, monoamine oxidase inhibitors (MAOIs), and neuroleptic drugs have been reported to be variably effective in borderline and schizotypal personality disorders (6, 7) and have direct or indirect effects on the serotonergic system (8–10).

If borderline and schizotypal personality disorders are related to obsessive-compulsive disorder, then treatment with fluoxetine might be effective in these conditions as well. Similarly, if impulse control problems arise from serotonergic dysregulation (6), fluoxetine might help control the disorder. Thus, a nonblind, prospective study was initiated to test the efficacy of fluoxetine in patients with borderline or schizotypal personality disorder or both.

## METHOD

Twenty-two outpatients satisfying the *DSM-III-R* criteria for borderline or schizotypal personality disorder or both underwent a prospective, nonblind trial of fluoxetine. All of the patients had come for psychiatric evaluation of anxiety or depression without being recruited. Eight of the individuals had primarily borderline personality disorder, 10 had both borderline and schizotypal disorders, and four had primarily schizotypal disorder. Thirteen of these patients also met the criteria for major depression at the time of entry into the study.

All of the subjects gave informed consent and completed two self-assessment questionnaires. The first was a short questionnaire assessing self-mutilation, and the second was the Hopkins Symptom Checklist (HSCL). The mutilation questionnaire asked patients to quantify their self-injurious behavior. The HSCL is a widely used

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test for assessing psychiatric well-being and has been used in other clinical trials involving borderline patients (6). These ratings were repeated every 3 weeks during the study. Ten patients were engaged in psychotherapy, but except for the brief medication visits (15–30 minutes) every third week, no changes were made in any of the psychotherapeutic interventions. Seven of these patients were receiving supportive psychotherapy, and three were receiving cognitive therapy.

The patients were responsible for financing their clinical visits and for purchasing their own medications. Eighteen of the 22 patients had previously failed trials of benzodiazepines, 16 were resistant to tricyclic antidepressants (no one had been taking clomipramine), 14 had failed to respond to neuroleptics, and nine were lithium nonresponders. Three of the individuals had not responded to trials of fluoxetine at doses of 60 mg or less, four had not been responsive to carbamazepine, three had not responded to valproic acid, and two had failed to respond to MAOIs. Only one of the patients had not taken any drug.

Thirteen of the subjects were female and nine were male. Their mean±SD age was 34.4±6.9 years; the mean±SD duration of illness was 18.1±10.2 years.

Fluoxetine was started at a dose of 20 mg/day and increased by 20 mg every third day to a maximum of 80 mg. This dose reduced the risk of undermedication and thus would help to guarantee a fair trial. There was no washout period before fluoxetine therapy began. The only other medications the patients were allowed to use were lorazepam (2 mg) and chloral hydrate (1000 mg) for insomnia. Four other individuals who initially entered the study along with the 22 subjects did not return for their 3-week appointments. We do not know why they chose to discontinue treatment, as efforts to contact them were unsuccessful. Their self-mutilation episodes and HSCL scores are not included in the data we report, and they were considered treatment nonresponders. Loss of patients to follow-up is a problem in many studies involving this diagnostic population (2, 6).

Self-mutilation was defined as an active history of cutting oneself during the 6 weeks before the study. Multiple cuts over a 12-hour period were recorded as a single event. Thus, the maximal possible number of episodes per individual per week was 14. The number of individual cuts per event varied from one to 16. No physical examinations were performed to check changes in self-mutilation.

Outcomes were assessed by comparing self-mutilation reports and HSCL scores at each of the follow-up visits (at 3, 6, 9, and 12 weeks). Persons with these types of personality disorders are often poorly compliant with follow-up appointment schedules, and some of the subjects did not have all four of their follow-up visits. All of the patients, however, had tests at 0 and 12 weeks. Instead of eliminating cases where one test was missed, and thus possibly biasing our outcome results, we used a three-factor, split-plot design to test hypotheses. The factors were time (weeks 0 and 12), depression (present or absent), and personality subtype (borderline and/or schizotypal). The design was not balanced, since combinations of depression and personality type occur with different frequencies. A Bonferroni correction was used to determine statistical significance of scores on the five subscales of the HSCL.

## RESULTS

Twelve of the 22 patients reported self-mutilating behavior. Of these 12, three met the criteria for borderline disorder, two for schizotypal disorder, and seven for both. These 12 patients had a mean±SD of 4.1±4.0 incidents of mutilation per week for at least 6 weeks before entering the study. This represents a total of 49 mutilative episodes overall. The incidence of mutilation at 3 weeks (11 patients, 42 episodes) and 6 weeks (11 patients, 40 episodes) was not markedly different from the values at the beginning of the study. By 9 weeks, however, 50% fewer individuals (N=6) were self-injurious, and the total number of mutilative episodes had decreased to 13, a 74% reduction. Only two of the 12 patients were still engaged in cutting at the end of the 12 weeks of fluoxetine therapy, and this occurred less than once per week (0.75 episodes), a 97% reduction.

The HSCL data are given in table 1. The mean±SD score for all 22 patients at entry into the study was 197.3±60.1. The mean scores at 3 weeks, 6 weeks, and 9 weeks indicate a progressive decline. Many of the subjects, however, had higher scores at one of the later times than at the previous one. While the majority of patients showed a progressive decline in symptom scores, it was not until 12 weeks that patients consistently noted improvement. The mean HSCL score at 12 weeks was significantly lower than the score at baseline. No interaction between time and mood ($F=0.002$, $df=1, 16$, $p<0.32$), between time and personality ($F=0.04$, $df=2, 16$, $p<0.96$), or among all three variables ($F=0.26$, $df=2, 16$, $p<0.91$) was found.

The changes in HSCL scores were similar in the patients with borderline personality disorder, the patients with schizotypal disorder, and the patients with both diagnoses. No statistical difference based on diagnosis could be found ($F=0.26$, $df=2, 16$, $p<0.98$), nor was there any interaction of personality diagnosis with mood state ($F=0.01$, $df=2, 16$, $p<0.39$) or time (as mentioned above), or among all three variables (as mentioned above).

The presence or absence of major depression did not appear to affect outcome. The improvement in HSCL total score of the nondepressed patients was not statistically different from that of the depressed patients (table 1). The depressed patients did have significantly higher scores than the nondepressed patients at entry into the study. No mood interactions with time, personality, or both were found to be significant.

These same results were evident for particular symptom subset patterns on the HSCL for the group as a whole (table 1). Ratings on the obsessive-compulsive,

**TABLE 1. Changes in Self-Mutilation and Hopkins Symptom Checklist (HSCL) Scores of Patients With Borderline and/or Schizotypal Personality Disorder During a 12-Week Trial of Fluoxetine**

| | Week | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | | 3 | | 6 | | 9 | | 12 | |
| Measure | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Mutilations per week by self-injurious patients | 4.1 | 4.0 | 3.8 | 4.0 | 3.6 | 3.5 | 2.2 | 2.0 | 0.4 | 0.2 |
| HSCL score (total) | | | | | | | | | | |
| All patients (N=22)[a] | 197.3 | 60.1 | 170.0 | 51.3 | 139.2 | 53.0 | 102.9 | 39.3 | 69.5 | 44.7 |
| Borderline patients (N=8) | 204.1 | 64.1 | 198.8 | 38.2 | 154.5 | 57.2 | 97.0 | 12.4 | 75.3 | 50.3 |
| Schizotypal patients (N=4) | 159.8 | 39.6 | 132.0 | 59.3 | 68.0 | 39.2 | 86.0 | 63.4 | 52.5 | 30.4 |
| Patients with both borderline and schizotypal disorder (N=10) | 206.8 | 54.4 | 164.4 | 53.6 | 150.9 | 32.4 | 118.2 | 31.1 | 68.5 | 29.4 |
| Depressed patients (N=13)[b] | 226.2 | 56.7 | 177.6 | 55.1 | 173.2 | 29.8 | 115.4 | 27.4 | 81.3 | 41.8 |
| Nondepressed patients (N=9) | 155.4 | 36.4 | 161.3 | 43.5 | 90.7 | 38.6 | 90.4 | 47.2 | 49.7 | 27.0 |
| HSCL subscale scores (all patients, N=22) | | | | | | | | | | |
| Obsessive-compulsive[c] | 25.1 | 7.3 | 22.9 | 7.6 | 20.5 | 7.7 | 16.4 | 6.9 | 10.9 | 7.2 |
| Interpersonal sensitivity[d] | 22.6 | 7.8 | 19.8 | 8.5 | 16.9 | 6.9 | 13.2 | 6.3 | 7.8 | 4.6 |
| Depression[e] | 37.0 | 7.3 | 33.2 | 9.8 | 26.6 | 9.6 | 19.2 | 6.6 | 12.0 | 7.7 |
| Anxiety[f] | 23.5 | 9.3 | 22.5 | 10.3 | 17.5 | 9.4 | 11.5 | 6.3 | 8.6 | 6.2 |
| Paranoid ideation/psychoticism[g] | 28.1 | 13.3 | 22.3 | 9.9 | 18.4 | 9.0 | 15.9 | 8.2 | 9.4 | 7.3 |

[a] Significant difference between week 0 and week 12 (F=14.38, df=1, 16, p<0.001).
[b] Significant difference between depressed and nondepressed patients at week 0 (F=1.12, df=1, 16, p<0.006).
[c] Significant difference between week 0 and week 12 (F=67.18, df=1, 20, p<0.0001).
[d] Significant difference between week 0 and week 12 (F=81.64, df=1, 20, p<0.0001).
[e] Significant difference between week 0 and week 12 (F=130.94, df=1, 20, p<0.0001).
[f] Significant difference between week 0 and week 12 (F=62.07, df=1, 20, p<0.0001).
[g] Significant difference between week 0 and week 12 (F=50.85, df=1, 20, p<0.0001).

interpersonal sensitivity, depression, anxiety, and combined psychoticism and paranoid ideation subscales all declined significantly from baseline to week 12, and no effects of mood and/or personality on outcome were found (data not shown).

We used a method described by Goldberg et al. (6) to address the question of clinically significant change. These authors noted that a convention has developed in which "a change of 0.50 standard deviation (SD) units is 'clinically significant' and a change of 0.75 or more SDs is among the largest one can expect to observe" (p. 683). They used the baseline standard deviation as the unit requiring change to satisfy these requirements. According to these criteria, the change in mutilative behavior was 1.0 SD, and the overall change in total HSCL score was 2.1 SD. The changes in obsessive-compulsive (1.9 SD), interpersonal sensitivity (1.9 SD), depression (3.4 SD), anxiety (1.6 SD), and psychoticism/paranoid ideation (1.4 SD) ratings were all well above the criteria of Goldberg et al. (6) for clinical significance. The group averaged a 65% decrease in their HSCL scores, and no patient's condition worsened with treatment (data not shown).

## DISCUSSION

Twenty-two (85%) of 26 patients with borderline and/or schizotypal personality disorder completed a 12-week course of fluoxetine treatment at a dose of 80 mg/day. The individuals studied had chronic illnesses averaging 18.1 years in duration that had proven unresponsive to a variety of other treatment modalities. There was a statistically and clinically significant decrease in symptoms. Thus, this preliminary study suggests that fluoxetine is useful in the treatment of borderline and schizotypal personality disorders.

The results must be viewed cautiously, however, because of the open nature of the trial, the lack of a clinician assessment scale, and the lack of a control group. This leaves open the possibility that the improvement was related to nondrug factors. However, the subjects had not responded to any previous drug treatment or psychotherapy. Second, the chronicity of illness and the multiplicity of failed previous treatments made the response to fluoxetine impressive. Third, a follow-up evaluation of the 22 patients who responded and remained on a fluoxetine regimen (mean±SD duration=24.7±15.4 weeks) showed continued improvement. Fourth, even allowing for a placebo effect as large as 1.0 SD, changes greater than this were noted, which are clinically significant according to the criteria of Goldberg et al. No interactions between time and either mood classification or personality subgroup were significant. This indicates that although differences between depressed and nondepressed groups are shown by the HSCL scores, the patterns of change are not statistically different. This further suggests that the generality of our conclusions need not be conditioned by diagnostic group. The small sample size, however, indicates the need for further study of this issue.

This study used objective rating scales to evaluate the efficacy of fluoxetine in patients with *DSM-III-R*-identified borderline and schizotypal personality disorders. The study needs to be followed by a double-blind, placebo-controlled study. The possibility that some of the patients will no longer fulfill the *DSM-III-R* criteria for axis I and II diagnoses after treatment needs to be evaluated. Biological studies assessing serotonergic function in these disorders would be relevant. It is quite possible that the apparent efficacy of fluoxetine in these two disorders does not signify a particularly important role of serotonin in the etiology of the disorders and that neurotransmitters other than serotonin are important.

In summary, this study using objective rating scales documented the efficacy of fluoxetine in borderline and/or schizotypal personality disorders. The treatment modalities that have been reported to be effective in these disorders might be active, in part, through an effect on the serotonergic system. The results reported here suggest that borderline and/or schizotypal personality disorders may represent serotonin dysregulation.

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# Manic Syndrome in AIDS

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*A manic syndrome in eight patients with AIDS is described. On the basis of clinical, neuropsychological, laboratory, magnetic resonance imaging, and epidemiological evidence, the authors suggest that the manic syndrome was secondary to HIV infection. The patients also developed concomitant cognitive impairment.*

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In this article we retrospectively review our experience with eight AIDS patients who developed a manic syndrome. Several authors reported that mania can be a presenting feature of patients with AIDS (1–5). The majority of these patients had some degree of cognitive abnormality suggestive of HIV-related cognitive impairment (6). Unfortunately, the previous reports had limited laboratory and imaging data, and none included magnetic resonance imaging (MRI) findings.

Four criteria have been suggested for identifying psychiatric syndromes that are secondary to a neuropathological disorder: 1) presence of a defined clinical syndrome, 2) identification of other major disease manifestations, 3) evidence of active cerebral disease, and 4) increased prevalence of the syndrome in the population with the disorder (E.D. Caine, unpublished manuscript, 1990). We provide clinical, neuropsychological, laboratory, imaging, and epidemiological data that fulfill these criteria. These data support the hypothesis that the manic syndrome in these patients is secondary to HIV infection.

## METHOD

We reviewed all of the cases of individuals with AIDS who were admitted to the inpatient services of a hospital department of psychiatry from Aug. 1, 1986, through April 1, 1990. Individuals were classified as having a manic syndrome if they met the *DSM-III-R* criteria for a manic episode, with the exception of the organic etiology exclusion.

All of the eight patients who met diagnostic criteria for AIDS and had a manic syndrome underwent comprehensive evaluations, including lumbar puncture and MRI of the head. Six patients underwent neuropsychological testing. Although the test batteries varied, all included tests of attention (digit span), memory (Rey Auditory Verbal Learning Test), cognitive flexibility (digit symbol, Stroop Interference Test), perceptual-motor speed (Trail-Making Test B), and spontaneous word production (controlled word association, e.g., “F-A-S”). All MRI studies were performed with a 1.5-tesla MRI scanner (General Electric, Milwaukee) with a standard head coil as a receiver. Following the routine scans, gedopentate dimeglumine (gadolinium), 0.1 mmol/kg, was administered intravenously over a period of 2 minutes to six patients.

## RESULTS

All of the eight subjects were men. One was black, one was Hispanic, and the rest were white. Their average age was 36.7 years (range=27–53 years). All of the patients had histories of homosexual contact; only two patients also had histories of intravenous drug abuse. The mean CD4$^+$ lymphocyte count at the time of admission was 60/mm$^3$ (range=10–170). Five patients had been taking zidovudine prior to admission, and one was started on the drug during hospitalization. No cause for a secondary affective disorder other than HIV infection was identified.

The eight patients had a characteristic course of illness. At the time of admission, the following symptoms were prominent: irritability (N=6), decreased sleep (N=6), pressured speech (N=5), grandiosity/euphoria (N=4), irresponsible spending (N=4), and racing thoughts (N=2). For most patients irritability was more prominent than euphoria. Four of the eight patients began lithium therapy, and six began neuroleptic treatment. Five of the patients had had a prior episode of depression beginning about the time of the initial HIV diagnosis. Three of these had adjustment reaction with depression, and two suffered a major

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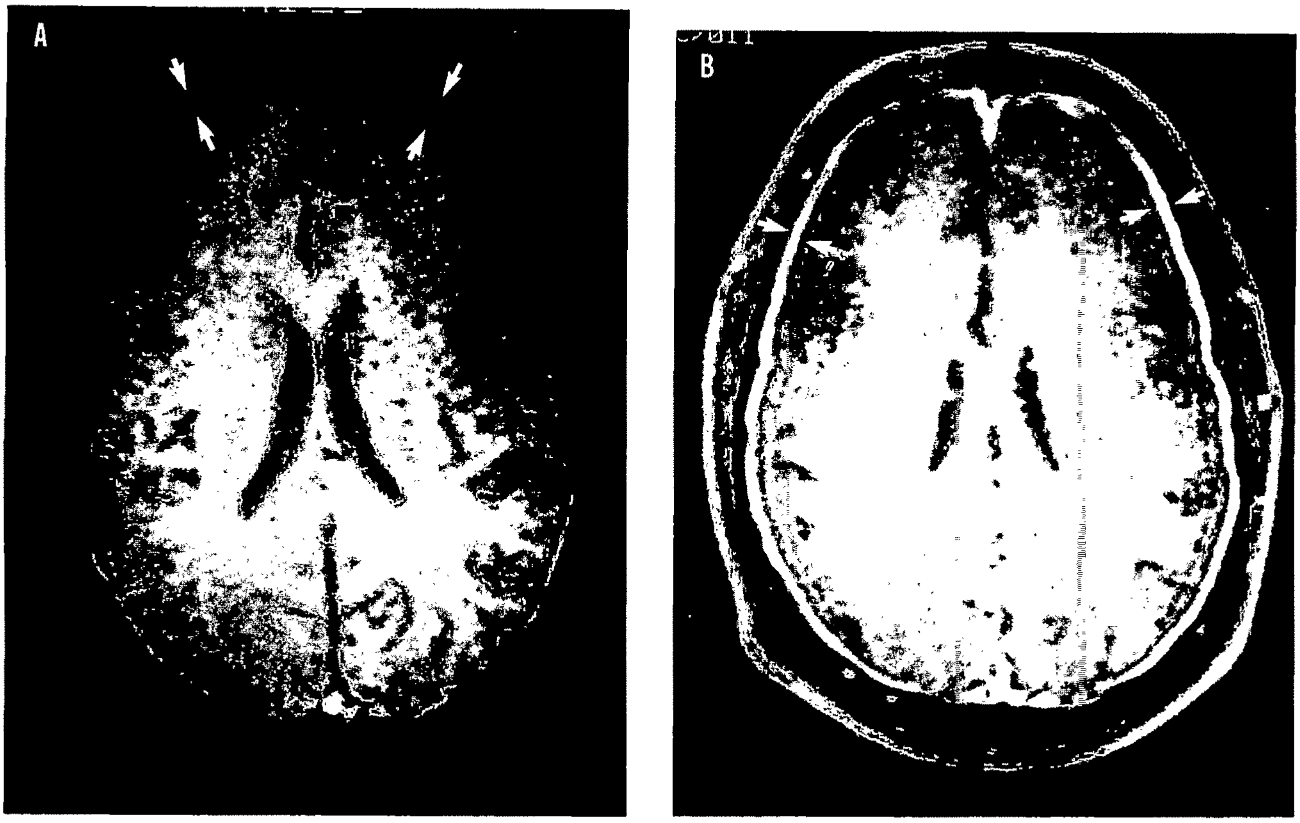
**FIGURE 1. MRI Scan Without (A) and With (B) Gadolinium Enhancement in a 41-Year-Old Homosexual Man With Mania**[a]



[a](A) Precontrast $T_1$ weighted axial image (TR/TE=600/20 msec) reveals thickening of the meninges (arrows). (B) Corresponding gadolinium-enhanced MRI image demonstrates marked enhancement of the thickened meninges (arrows).

depressive episode. Four of the five required antidepressant treatment.

Aside from the histories of depression, all of the patients were thought by their primary caregivers to have been cognitively normal before their psychiatric admission. Neuropsychological testing performed after the manic symptoms had abated revealed cognitive abnormalities consistent with HIV-related cognitive impairment. The most consistent findings in the six patients who underwent this testing were memory deficits (N=4), impaired cognitive flexibility (N=3), and slowed perceptual speed (N=3). In some patients these cognitive deficits were marked.

Lumbar punctures were performed on all patients. Two patients had mild CSF pleocytosis, and another two had mildly elevated CSF protein levels. Results of other CSF investigations were normal.

MRI scans of the head were abnormal for all eight patients. The primary findings were abnormalities in the regions of the fornix and corpus callosum (N=7), atrophy (N=4), and changes in white matter (N=2). No significant mass lesions were identified. In addition, four of the six patients who received intravenous gadolinium demonstrated cortical meningeal enhancement (figure 1). This finding was most pronounced in the patients with CSF pleocytosis. In contrast, there were no cases of meningeal enhancement at our center in another 28 concurrent gadolinium-enhanced MRI scans of HIV-infected patients without a manic syndrome (eight of whom also had CSF pleocytosis), a significant difference ($p<0.01$, Fisher's exact test, two-tailed).

All of the patients had considerable improvement in their mood disturbance during hospitalization, but their course was not typical for bipolar disorder. The irritability, sleeplessness, and pressured speech improved in all, but there was often persistent distractibility and poor judgment. The residual symptoms may have been, in part, due to the persisting cognitive impairment.

The lifetime risk for a manic episode in men of this age is approximately 1% (range=0.4%–1.6%) (7). Given the shortened life span of AIDS patients, this figure probably overestimates their lifetime risk. The reported population of similarly aged men with AIDS in the catchment area for the hospital was 190 as of April 1, 1990. According to the estimate of lifetime risk for a manic episode, two cases of mania would have been expected in a population of this size. The observed eight cases is outside the 95% confidence interval (0.24–7.22) for the number of expected cases based on the Poisson distribution.

## DISCUSSION

These eight AIDS patients with a manic syndrome represent the largest such group reported to date. Our data support the hypothesis that the manic syndrome was secondary to AIDS. Each patient presented a characteristic syndrome that fulfilled clinical diagnostic criteria. As a group they demonstrated typical manic symptoms such as decreased sleep, pressured speech, and disorganized thinking, although irritability was more common than a euphoric or an expansive mood.

In addition to the affective disturbance, a major manifestation was significant cognitive disorder. The deficits were consistent with previous reports of HIV-related intellectual impairment (8). Neuropsychological abnormalities are noted frequently during the late stages of HIV infection. Our patients had been followed closely by experienced clinicians. Both the manic symptoms and the cognitive decline were newly detected abnormalities, suggesting that the onset of the affective disorder coincided with the development of frank intellectual deterioration. The cognitive deficits persisted after the remission of the manic symptoms, suggesting that they were not epiphenomena of mania.

Clinical laboratory examinations provided evidence of active cerebral disease. The findings of CSF studies were frequently abnormal, and all of the MRI scans were abnormal. In addition, four of the six patients given gadolinium-contrast injections demonstrated enhancement of the cortical meninges. Last, we noted an increased prevalence of manic episodes in the county's AIDS population.

All four criteria for identifying a secondary psychiatric syndrome were fulfilled. Our results suggest that the manic syndrome in these AIDS patients was a secondary disorder, one that was associated with rapidly emerging cognitive decline. This syndrome may represent an intensification of cerebral viral activity or its immediate sequelae (9). Clinicians should recognize that although the manic symptoms typically respond to standard treatments, the unremitting cognitive impairment makes the long-term care of these patients challenging.

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# Decrease in Resting Metabolic Rate During Abstinence From Bulimic Behavior

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*Among eight normal-weight bulimic women studied during 1 week of binge eating and vomiting and 7 weeks of abstinence without weight loss, resting metabolic rate and $T_3$ and $T_4$ levels fell significantly during abstinence. These data suggest that a physiological consequence of binge eating and vomiting is an increase in metabolic rate, in part due to increased thyroid hormone activity.*

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Patients with bulimia nervosa have an abnormally low resting metabolic rate, which is the largest component of daily energy expenditure (1, 2). As a consequence, it is likely that bulimic persons gain weight easily and therefore feel compelled to diet and engage in behaviors that raise the resting metabolic rate, such as rigorous exercise (3). In the present study, we attempted to determine whether binge eating and vomiting also increase the resting metabolic rate. To date, women with bulimia have been studied during inpatient hospitalization, when they are restrained from binge eating and purging, or as outpatients, when their bulimic behaviors cannot be reliably quantified or controlled. We studied the resting metabolic rate of eight bulimic patients during a week of active binge eating and vomiting in the hospital and compared it to the rate during abstinence in the hospital. Along with catecholamines, thyroid hormone is a major determinant of resting metabolic rate (4), so we assessed thyroid indices during both the binge eating and abstinence phases.

## METHOD

The subjects were eight normal-weight bulimic women admitted to the Clinical Center of the National Institutes of Health. They met the *DSM-III-R* criteria for bulimia nervosa and were 83%–107% of average body weight (5). Informed consent was obtained from all subjects. Their mean±SD age was 23.4±2.5 years, the mean duration of illness was 6.5±3.0 years, and the mean frequency of binge eating was 21.3±22.4 episodes per week. The subjects abstained from taking any medication and from aerobic exercise for at least 1 month before admission. They continued their binge eating and vomiting during the first week of hospitalization. All subjects selected their own food throughout the hospitalization, although they were required to keep their weights within 1 kg of their admission weights. All subjects binged at least once per day during the first week and vomited after each binge. After the first week, the subjects were closely supervised to enforce abstinence from binge eating and purging for the next 7 weeks. Exercise was limited to 15 minutes of aerobic exercise three times per week.

After an overnight fast, resting metabolic rate was measured between 7:00 a.m. and 8:00 a.m. by indirect calorimetry. To reduce variability, the rate was measured over 15 minutes on four mornings during the week of active binge eating and purging and on four mornings 1–2 weeks apart during abstinence.

Caloric intake was calculated on the 4 days preceding measurement of the resting metabolic rate, as previously described (2). Plasma $T_3$ and $T_4$ levels were obtained during the week of active binge eating and during week 7 of abstinence.

Differences between repeated measures in the binge eating and abstinence phases were analyzed with a two-way repeated measures analysis of variance (ANOVA). Differences among repeated measures within each phase were analyzed with univariate repeated measures ANOVA. When a significant F ratio was obtained for the difference between phases in the two-way ANOVA and there was no significant difference within each phase, differences between means were evaluated by univariate ANOVA and post hoc Scheffé F tests. Differences between single measures in the two phases were analyzed by paired t tests. Pearson product-moment

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correlations were calculated to determine relationships between variables. To estimate the variability of the resting metabolic rate, the mean intraindividual coefficient of variation was calculated for each phase. All values are given as mean±SD.

## RESULTS

The resting metabolic rate fell from 1136±258 kcal/day during the binge eating phase to 912±99 kcal/day during the abstinence phase (F=8.7, df=1, 15, p=0.02). Caloric intake decreased from 8425±4591 kcal/day to 1678±223 kcal/day (F=19.1, df=1, 15, p=0.004). The $T_3$ level dropped from 111±24 ng/dl to 95±12 ng/dl (t=2.4, df=7, p=0.05). The $T_4$ level also decreased, from 7.5±1.2 g/dl to 5.8±0.83 g/dl (t=5.3, df=7, p=0.001). There was no significant change in mean weight between the two phases (binge eating phase: 57.0±8.3 kg; abstinence phase: 57.1±7.2 kg; F=0.1, df=1, 15, p=0.81).

Change in resting metabolic rate did not correlate significantly with change in caloric intake, change in $T_3$ or $T_4$, duration of illness, or frequency of binge-purge episodes.

There was no significant change in resting metabolic rate over the four sampling times in each phase (binge eating phase: F=1.4, df=3, 31, p=0.27; abstinence phase: F=1.1, df=3, 31, p=0.37). The mean intraindividual coefficient of variation was 15% in the binge eating phase and 10% in the abstinence phase. There was no significant change in weight within each phase (binge eating phase: F=2.1, df=3, 31, p=0.12; abstinence phase (F=0.32, df=3, 31, p=0.81).

## DISCUSSION

Both resting metabolic rate and thyroid hormone measures decreased significantly during abstinence from binge eating and purging. Although thyroid hormone is known to be a determinant of metabolic rate (4), the lack of correlation between these measures in this study may be explained by the small number of subjects.

Because most food ingested during binge eating is vomited before it can be absorbed, the number of calories actually absorbed during days on which binge eating occurs is unknown. Since decreased caloric intake can decrease resting metabolic rate and thyroid function (6), it could be argued that decreased caloric absorption during the abstinence phase produced the findings reported here. However, in a study of 30 days of mild caloric restriction (6), which resulted in a decrease in resting metabolic rate half that seen in this study, nonbulimic subjects showed a small but consistent drop in weight. Thus, it is unlikely that the subjects in our study could have reduced their resting metabolic rate by lowering their caloric load without producing any change in weight.

Alternatively, preabsorptive responses to the food consumed during binge eating are more likely to contribute to the higher thyroid hormone levels and resting metabolic rate in the binge eating phase. Acute food ingestion without absorption could increase metabolic rate by the known preabsorptive release of insulin (7), which leads to activation of the sympathetic nervous system (8). In support of this model is the finding that bulimic subjects show an exaggerated release of insulin (9) and catecholamines (10) during binge eating but glucose elevations that are similar to those seen in normal subjects after a large meal (9). Overfeeding is also known to activate the thyroid axis, which can in turn increase the metabolic rate (4), but whether this can occur through preabsorptive mechanisms alone remains to be determined. In this regard, the finding that the change in resting metabolic rate with abstinence did not correlate with change in caloric intake is not too surprising, since the size and frequency of binges varied widely among the patients.

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# The Course of Psychological Symptoms After Resolution of Lawsuits

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*The authors show that factors associated with a better psychological outcome after an accident and the resulting litigation include a longer time after resolution of the litigation, a shorter time between injury and resolution of the litigation, and less severe initial psychological symptoms.*

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We live in an increasingly litigious society, where victims of accidents bring lawsuits and often claim that they have suffered accident-related psychological symptoms. Psychiatrists are frequently asked by defense and plaintiff attorneys to evaluate accident victims and determine the extent of psychological damage and the eventual prognosis of postaccident symptoms (1, 2). Nevertheless, there has been a paucity of follow-up studies on litigants, and the few existing studies have generally not used standardized assessment procedures (2–5).

In this article we report on a follow-up study of litigants that used standardized interviews and rating scales to assess current and past functioning and to determine accurate *DSM-III-R* diagnoses. The study focused on the following questions. 1) What is the course of postaccident psychological symptoms after resolution of a lawsuit? 2) What factors are associated with good and bad outcomes?

## METHOD

All of the subjects had been evaluated by one of the authors (M.R.T.) in the course of lawsuits. Subjects were included if they 1) had been victims of industrial or motor vehicle accidents, 2) had instituted civil litigation that had been resolved by the time of the study, 3) had complained of psychological symptoms resulting from the accidents during the course of the litigation process, and 4) had valid addresses in their charts and therefore could be contacted. On the basis of these criteria, 25 potential subjects were contacted by letter and follow-up phone calls. Seven subjects could not be interviewed because they did not respond to the letter (N=2), were too busy (N=2), did not keep the appointment for the interview (N=1), or felt it would be too traumatic (N=2). Eighteen (72%) gave informed consent and were interviewed.

Before being interviewed, each subject completed a general 90-item self-report symptom inventory, the SCL-90-R (6), and a 15-item self-report inventory of symptoms of posttraumatic stress disorder, the Impact of Event Scale (7). Both questionnaires were completed twice: for the past week and for the time that the subject had the most symptoms. Then, to make an accurate *DSM-III-R* diagnosis, the interviewer (R.L.B.) conducted the Structured Clinical Interview for DSM-III-R—Nonpatient Version (8) with an additional posttraumatic stress disorder module. She also conducted the Mini-Mental State examination (9) for each patient to screen for cognitive deficits and completed the Global Assessment of Functioning Scale (GAF Scale) (*DSM-III-R*, p. 12) to measure overall psychiatric impairment.

## RESULTS

At the time of their interviews, the 18 subjects had a mean±SD age of 49.80±10.83 years (range=30–68 years). Thirty-three percent (N=6) were female. Sixty-one percent (N=11) were married, and all were Caucasian. Sixty-seven percent (N=12) had worked as skilled or unskilled manual workers or clerical workers. Fifty-six percent (N=10) were currently employed; all of these 10 had resumed employment before settlement of their lawsuits. Only one subject had

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**TABLE 1. Pearson Correlations of 18 Plaintiffs' Current Global Assessment of Functioning Scale Scores With Aspects of Their Clinical Histories and the Litigation Process**

| | | | | Correlation With Global Assessment of Functioning Scale Score[a] | |
|---|---|---|---|---|---|
| Variable | Mean | SD | Range | r | p |
| SCL-90-R global severity index[b] | 1.71 | 0.81 | 0.48–3.12 | −0.50 | 0.04 |
| Impact of Event Scale | | | | | |
| Avoidance subscale score[b] | 20.39 | 11.72 | 0–40 | −0.60 | 0.01 |
| Intrusion subscale score[b] | 26.56 | 10.56 | 0–18 | −0.43 | 0.07 |
| Years from injury to settlement | 4.73 | 1.81 | 2.23–8.68 | −0.50 | 0.03 |
| Years from settlement to interview | 2.45 | 1.69 | 0.14–5.73 | 0.55 | 0.02 |
| Years from injury to interview | 7.18 | 2.28 | 2.41–11.30 | 0.01 | n.s. |

[a] A negative correlation between the variable and this score means that as the variable (e.g., years from injury to settlement) increased, the score decreased. A positive score indicates the opposite tendency. Lower scores on the Global Assessment of Functioning Scale indicate more severe overall psychiatric impairment.

[b] Rated for the period after the litigated injury during which symptoms were worst. Higher numbers indicate more severe symptoms.

a history of a mental disorder before the accident (major depression).

At the time of their accidents, 67% (N=12) of the subjects had mild physical injuries, and 33% (N=6) had severe physical injuries (defined as being life threatening). The median damage award was $40,000 (range=$0–$360,000).

At the time of the research interviews, no subjects showed gross cognitive deficits, as indicated by their Mini-Mental State scores falling in the normal range (mean±SD=29.3±1.36, range=25–30). In addition, at the time of the interviews, the mean GAF Scale score was 75.0±13.17 (range=55–90), which indicates "some mild symptoms . . . or some difficulty in social, occupational, or school functioning . . . but generally functioning pretty well" (*DSM-III-R*, p. 12).

We evaluated the course of psychological symptoms on the basis of changes in diagnosis, Impact of Event Scale scores, and SCL-90-R scores. After their accidents, 78% (N=14) of the patients had had episodes of one or more mental disorders, including major depression (N=11), posttraumatic stress disorder (N=10), alcohol abuse (N=2), conversion disorder (N=1), and panic disorder with agoraphobia (N=1). By the time of the research interviews, however, the proportion of the subjects with one or more mental disorders had decreased significantly to 44% (N=8) (Fisher's exact test, $p<0.02$). When ratings for the worst period after the accident and for the past week were compared by means of single-sample t tests, there were significant decreases in scores on the Impact of Event avoidance subscale ($t=-3.25$, $df=17$, $p<0.005$) and intrusion subscale ($t=-5.45$, $df=17$, $p<0.0002$) and on the SCL-90-R global symptom index ($t=-5.71$, $df=17$, $p<0.0002$). For 13 of the 18 subjects there was a decrease in symptoms on the avoidance subscale, for 15 of the subjects there was a decrease on the intrusion subscale, and for 17 of the subjects there was a decrease on the SCL-90-R global symptom index. Although all of the subjects were evaluated by psychiatrists during the course of litigation, only three subjects received ongoing psychiatric treatment. These three subjects had a current mean score of 58 (range=55–60) on the GAF Scale, which indicates moderate symptoms.

We computed correlation coefficients between the subjects' current level of overall psychiatric impairment (as indicated by the GAF Scale scores) and demographic variables, clinical history, and aspects of the litigation process. GAF Scale scores were not significantly correlated with age, gender, marital status, whether or not the subjects had returned to work, extent of physical injury, amount of compensation awarded, or scores on the Mini-Mental State examination. As shown in table 1, subjects who reported having had more severe symptoms after the injury, as indicated by the SCL-90-R global symptom index, the Impact of Event avoidance subscale, and (at the level of a trend) the Impact of Event intrusion subscale, had significantly more severe psychiatric impairment at the time of the research interviews.

No significant correlations were found between GAF Scale score and the total number of years from the injury to the interview. However, there were significant correlations indicating that a shorter time between the injury and the settlement was associated with less current psychiatric impairment and that a longer time from the settlement to the interview was also associated with less psychiatric impairment.

## DISCUSSION

Although some subjects developed chronic psychological problems after the injuries that resulted in litigation, for this sample of plaintiffs, follow-up after the settlement of litigation showed that most subjects eventually had substantial remission of psychological symptoms.

This study suggests that factors associated with a better outcome of psychological symptoms after an accident and the resulting litigation include a longer time after resolution of the litigation and a shorter time between injury and litigation. Although the correlational design of this study precludes causal inferences, one hypothesis which could explain this result is that the stress of the litigation process itself maintains or exacerbates psychological symptoms. If the plaintiff has a shorter time to endure the stress of litigation, the outcome is better. In addition, as more time passes after litigation is finalized, the plaintiff has more time to recover from the psychological stress of the accident and the litigation. It is interesting that the important factor is not the amount of time after injury but, rather, the amount of time relative to the settlement of the lawsuit. To our knowledge, this is the first study to show this finding.

Plaintiffs who had the most psychological symptoms after their injuries had the worst outcome on follow-up. Hence, severity of plaintiffs' initial psychological symptoms appears to be a risk factor in terms of the likelihood of having a poor outcome.

There are several potential limitations to this study, including small sample size, lack of a control group of accident victims who did not bring lawsuits (although in our litigious world, this group may be hard to find), and use of a cross-sectional assessment that relied on subjects' recollections of symptom course. In addition, the subjects were recruited from one center in England. The results may not be generalizable to other groups of litigants, but they are sufficiently promising to warrant further prospective studies with larger groups of plaintiffs.

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# Book Forum

## Nancy C. Andreasen, M.D., Ph.D., Editor

## ASPECTS OF PSYCHOANALYSIS

**The Multiplicity of Dreams: Memory, Imagination, and Consciousness,** *by Harry T. Hunt. New Haven, Conn., Yale University Press, 1989, 262 pp., $27.50; $12.95 (paper).*

Judging from the number of books that have been published in the last 5 years, I think dreams are back in fashion. The list ranges from the serious, science-based works of neurophysiologists J. Allan Hobson (1) and Jonathan Winson (2) to the popular clinical psychology "how to" books of Gayle M.V. Delaney (3) and Jayne Gackenbach and Jane Bosveld (4). Harry Hunt's book *The Multiplicity of Dreams* is like none of these. It does not offer a basic science approach to the mechanisms behind dreaming, nor does it offer a direct approach to their understanding and to the improvement of waking life based on this understanding. It is more a philosophy of dreaming than a treatise on either the science or the art of dreaming.

What Dr. Hunt offers is the sound reminder that dreams are infinitely varied experiences that cannot easily be described, let alone explained, by any one principle. Dr. Hunt takes the reader through a journey into previous theories of where and how dreams are organized and what they express; he offers a new way to make order out of their multiplicity. He proposes a three-dimensional diamond-shaped model: the vertical dimension represents vividness, from realistic to nightmare; the horizontal dimension represents the degree of symbolic differentiation; and the depth dimension represents the complexity of the story structure and physical setting. These are the formal properties Dr. Hunt proposes for describing and ordering all dreams. He tells us that there are mundane dreams and fantastic, pressure-discharge dreams; dreams based on somatic states and illness; and dreams based on esthetically rich metaphor, nightmares, and archetypal-mythological types. The many kinds of dreams may be open to many kinds of uses: embodying history and fictional narrative and generating metaphors from and for the dilemmas of waking life. "Any human situation, then, can be framed or taken as a metaphor for some other situation. But the closer we are to the direct living of a situation, the harder it is to turn around on and see it as a metaphor for something else" (p. 216). Dreams are a source of metaphor, illuminating and ordering "the teeming present" (p. 216).

Hunt is not a lucid writer. His expression of meaning is as convoluted as a dream. We wait and hope for a clarifying breakthrough sentence or two, and sometimes it comes: "Dreaming may indeed be an Ur-form for some very fundamental cognitive capacities, in particular the narrative story as sequential configuration fusing concordance and discordance, the transformation of one situation into an expression or metaphor for another, and the metaphysical questioning of the reality of our lives—the idea, known to all peoples in all times, that in some basic sense life *is* like a dream" (p. 214). That is as clear as it gets.

Is the struggle to follow this writer's search for order and meaning in the land of dreams worth it? It is a good antidote to the oversimplification of much of the present writing flooding the market. It tells us that the mind at night is not an open book, easy to read and manipulate at will. Dreams are a complex area still in need of the respect and awe owed to other levels of human functioning. This book will not offer much help to the practicing psychotherapist, but it might stimulate a few to the hard work of serious exploration of this expression of the mind.

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**The Creative Process: A Functional Model Based on Empirical Studies From Early Childhood to Middle Age,** *by Gudmund J.W. Smith and Ingegerd M. Carlsson. Madison, Conn., International Universities Press, 244 pp., $35.00.*

The creative process may seem mysterious and totally out of reach, but Drs. Smith and Carlsson have found a compelling new inroad with their "percept-genesis" assessment approach.

Our perceptions do not appear full-blown, the authors assert, but are the end result of a quick, complex subliminal process reflecting our individuality. Some patterns are more "creative" than others—showing "a generative or productive way of experiencing reality . . . . favored by open communication between different levels of experience" (p. 5). Even our most "objective" perceptions are colored, they say, by personality, including defenses, and by previous levels of mental organization and past experience. The percept-genesis model is compatible with dynamic theories such as psychoanalysis and with Piaget's cognitive genetic structuralism.

The percept-genesis method is designed to stretch out and dissect the perceptual "microprocess." A research subject, shown an image flashed on a screen for a mere 0.01 second and then for increasingly longer times (the "straight" percept-genesis), reports what is seen in each case. The subject does not know it is the same image and may well give changing reports. For example, the subject may report "two vague figures," "a man threatening a child," and "father threatening me" (at which point subthreshold anxiety and defenses lead to more conscious reconstructions of the image). After the image is recognized, it is then flashed on for shorter and shorter times (the "inverted" percept-genesis). The subject's report may now remain fixed or may change to include new or earlier interpretations ("two people dancing," "a man threatening a child"). Among proposed indicators of creativity, this changeability in the inverted percept-genesis is especially important, indicating "alternative views of reality." However, it is *intermediate* divergence that is tied most strongly to creativity—combining fanciful thought with ties to reality. (A comparison with psychotic perception would be interesting.)

Using the percept-genesis assessment, the authors have obtained a diversity of fascinating findings, including 1) greater imaginativeness is linked to relaxed (as opposed to focused) attention, 2) there are distinct styles of scientific thinking, 3) creativity is enhanced by a *slight* sharpening of anxiety, 4) the contention that true creativity is not possible until after age 4 is supported, 5) there are stages of greater and lesser creativity in later childhood and adolescence, 6) there are creative modes of managing aggressive material, and 7) there are patterns of psychological defense that facilitate or inhibit creativity.

This research approach shows innovative freshness and could open up many new avenues of investigation. However, the first question we must ask of any measure involves validity. The authors spend too little time on evidence that their percept-genesis assessment approximates the actual perceptual process; they refer readers elsewhere. Contrasts with conventional projective tests such as the Rorschach (also scorable for creativity) could also be useful. We also need more systematic demonstration that an aspect of "creativity" is being assessed. Some discussions seem to assume validity too readily. Empirical evidence of validity is available throughout the book but is not collected and evaluated as such until a brief section at the end. This evidence includes correlations of percept-genesis measures with independent criteria for creativity in art, science, and humanities (concurrent validity) and association with variables suggested by hypotheses from the creativity literature (construct validity). Many of the relevant studies also involve small samples. Future replications of this work will be important.

This is not a book for casual reading. It is a serious and technically detailed series of research reports. The presentation is at a fairly abstract level, and the frequent use of abbreviations can be taxing. Nonetheless, this book represents an important contribution to the creativity literature. It is essential reading for the serious student of creativity and a valuable resource for anyone who wants to know more about the creative process.

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**The Middle Years: New Psychoanalytic Perspectives,** *edited by John M. Oldham and Robert S. Liebert. New Haven, Conn., Yale University Press, 1990, 331 pp., $30.00.*

*The Middle Years* contains the well-written, carefully edited reflections of a group of psychoanalysts contemplating both the many years between age 35 or 40 and old age and the present contentious time in the story of analysis itself, between its youth in this century and its future.

The contentions spring from new views of women's development, homosexuality, the centrality of childhood, and the emergence of selfhood, authenticity, and values as central topics in psychoanalysis. The last represents part of the growing existential influence, not only on analysis but on the culture at large, in which meaning challenges cause, values and aspirations challenge the preoccupation with wishes, and self challenges the structures hitherto dominating orthodox thought. A desire to be comes to dispute the desire for objects. At last, the ego ideal as a leading factor in psychic life has its time in the sun. A concern with "psychic aliveness" is the principal form these developments take in the present book, especially the theme of coming to life or death in middle age. Such ideas still struggle to enter the systematics of analysis, despite the help of Winnicott. What is the true or authentic self? How is it recognized and achieved? The middle years raise these issues perhaps more poignantly than even adolescence does.

The theme of coming to life in middle age is balanced by the need to come to terms with illusions, limitations, and death itself in the same period. For Elliot Jaques, whose work lies near the heart of this book, the central problem of middle age is the fact of death. Paradoxically, the fact of death can set in motion a coming to terms that will sometimes be a coming to life in the face of death.

The authors use many other models of lifelong change—Eriksonian stages and tasks, evolving defensive styles, the reworking of childhood themes, and the concept of successive individuations, the first in childhood, the second in adolescence, and the third in the middle years. Levinson's dialectical view would have been a useful contrast to this theme of progress, but it receives short shrift. The discussion of individuation also suffers from Jung's continuing exile.

I believe this book points toward the maturation of psychoanalysis, when, for example, the worship of Freud recedes to the point that he remains a greatly creative figure but, like Newton, only a starting point for unpredictable developments. My own guess is that psychoanalysis will lose its definition by couch, hours, and even transference or interpretation to become the main contender with psychotherapy as the name for serious study and treatment by psychological means.

Ogden Nash quipped, "Middle age is the time of life a man first notices in his wife." Happily, *The Middle Years* will help move us beyond that point.

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**The Mourning-Liberation Process, Vol. I,** *by George H. Pollock, M.D., Ph.D. Madison, Conn., International Universities Press, 1989, 397 pp., $50.00.*

**The Mourning-Liberation Process, Vol. II,** *by George H. Pollock, M.D., Ph.D. Madison, Conn., International Universities Press, 1989, 320 pp., $37.50.*

This two-volume compilation of papers originally published between 1961 and 1986 represents George Pollock's 30-year inquiry into what he terms the "mourning-liberation process." A well-known psychoanalyst and past-president of APA, Dr. Pollock speaks with authority and clarity. Although his perspective is psychoanalytic, he draws impressively from history, cultural anthropology, ethology, biology, philosophy, theology, and literature to give proper weight to his monumental subject. There are approximately 500 references and a comprehensive index.

Volume I is composed of three parts: Introduction, Anniversaries and Time, and Aging. Its 16 chapters present a vast amount of descriptive material related to loss and mourning interwoven with theoretical tenets and analyses, including many compelling clinical examples. Particular emphasis is placed on the impact of sibling loss and on the various manifestations of anniversary reactions, areas in which Dr. Pollock has made seminal contributions.

Dr. Pollock's theoretical sensibilities appear to reflect a classical ego psychological framework, but he necessarily emphasizes those works of Freud, such as *Mourning and Melancholia* (1), which pertain to object relations and thus foreshadow more contemporary interpersonal and relationally informed psychoanalytic models (2). In this vein, he also makes fluent reference to the work of Melanie Klein, Jacobson, Mahler, Bowlby, and Kohut.

It is difficult to summarize Dr. Pollock's richly detailed constructs, but, simply put, he offers that object loss initiates a multi-stage mourning process for which there is a spectrum of normal and pathological outcomes. There may be resolution, potentially with great personal achievement; developmental arrest and/or fixation; or depression, melancholia, and possible suicide. He wisely concludes that the specific nature of response to loss is a complex function of an individual's age, state of ego development, previous experience, and ongoing interpersonal and social contexts.

The second volume, focusing on the creative resolution of mourning, contains psychobiographical portraits of a variety of creative artists, social figures, and thinkers, including Lenin, Simon Bolivar, Gustav Mahler, Kathe Kollwitz, Jack Kerouac, James Barrie, Thomas De Quincey, H.H. Monro (Saki), George Orwell, Rudyard Kipling, Patrick White, Wilfred Bion, Bertha Pappenheimer (Anna O.), and Josef Breuer (in the context of treating Anna O.). These narratives are particularly inviting because of the eminence of their subjects and make for pleasurable reading and contemplation.

Dr. Pollock's prose is lucid; he writes to be readily understood and, for the most part, avoids undefined technical terms and obscure allusion. Psychiatric professionals will have greater familiarity with his theoretical underpinnings, but educated lay readers will be comfortable as well. The text's encyclopedic quality, however, and the fact that the chapters were originally autonomous papers create considerable redundancy. There are also numerous excursions—into the nature of theory, for example, and the psychoanalytic understanding of affects—that, although intriguing, appear somewhat gratuitous.

Although this collection convincingly demonstrates the centrality of loss and struggle for reparation to the human condition and the ways in which character may crystallize around these experiences, a number of important issues are not critically digested. For example, there is little attempt to decipher why one person may find creative liberation from loss, another may commit suicide, and yet another, as in the example of Sylvia Plath, may both create great art and end her life by suicide. Although Dr. Pollock makes it poignantly clear that loss and mourning have thematic resonance in creative achievement, his implication of causality is not well developed, nor is there much critical discussion of the evaluations of this hypothesis by others (3).

There is also a paucity of systematic empirical study. Dr. Pollock consistently provides analyses of anecdotal material that "ring true" but remain shrouded in mysterious authority. This is an ongoing dilemma in psychoanalytic scholarship (4). Empiricism per se should not be valued over interpretation, but the current work, despite Dr. Pollock's invocation of "the canons of science," often seems more impressionistic than interpretive. Similarly, the application of psychoanalytic theory to biography and literature has its own dangers—from reductionism to frivolity—which the examples in these volumes risk, at times perilously.

Finally, there is little integration of the mourning-liberation process with contemporary clinical perspectives. Object relations theory as it pertains to borderline pathology (5), including a growing literature on early loss in these patients, is not addressed. The relevance of posttraumatic stress disorder is mentioned only in passing, and Mardi Horowitz's cognitive psychoanalytic approach to mourning (6), which complements Dr. Pollock's views, is not cited.

Despite these criticisms, Dr. Pollock's work affords a series of powerful lenses through which we can view a most profound aspect of human experience. Portions of the books will be valuable to clinicians as well as to individuals interested in applied psychoanalysis, the creative process, and the origins of cultural phenomena. Readers will be moved, perhaps hauntingly, to reflect on the enduring significance of loss in their own lives.

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## STRESS AND STRESS DISORDERS

**Too Scared to Cry: Psychic Trauma in Childhood,** *by Lenore Terr, M.D. New York, Harper & Row, 1990, 365 pp., $21.95.*

Lenore Terr has contributed perhaps more than any other single person to establishing the knowledge that childhood trauma exists, that it produces an enormous range of serious consequences in an almost endless array of forms, and that the treatment of these disorders ranges in efficacy from easy success to impossible. In the first chapter of *Too Scared to Cry* she notes the startling paucity of studies of childhood trauma, and she relates this to the lingering effects of Freud's turn from the childhood seduction theory to the role of early fantasies in the genesis of neuroses. Despite isolated studies here and there, important as they were, very little research was done on the effects of childhood disaster before the 1970s. Thus, when Dr. Terr was invited to work with a group of 26 children who had been kidnapped and buried alive for 18 hours—the Chowchilla kidnapping of 1976—she felt, rightly, that she was in a unique position to pioneer an important scientific study. She performed that study, which included many interviews with the children and their parents, the selection and study of a control group of nontraumatized children from nearby communities, and a 5-year follow-up on both groups.

Many of the extensive and fascinating findings were unexpected, such as that 10 of the 25 children in the control group demonstrated clear signs of posttraumatic symptoms. This discovery underscores Dr. Terr's belief that childhood trauma is not only far more damaging but also far more common than previously imagined and that for the most part ignorance and minimization of the problem prevails.*Too Scared to Cry* includes extensive data from the Chowchilla study as well as accounts from the records of well over 200 other children and adults seen by Lenore Terr in consultation and treatment. In addition, she draws anecdotal material from the professional literature, popular books, movies, and the news media to further document her main theses. Much of this material is absolutely spellbinding, but in the end I felt slightly traumatized by the sheer mass and variety of information about childhood trauma and its consequences. The fact that Dr. Terr attempts in one book to address both lay and professional audiences adds further difficulty, since she shifts her voice from simple explanations in a warmly personal manner to technical and theoretical discussions. Obviously the book's value as source material is both enhanced and limited by the volume of anecdotal material—enhanced by the variety and limited by the brevity of most clinical accounts.

Dr. Terr has approached the daunting task of organizing her data by dividing it into four clinical aspects of response to childhood trauma: the emotions, the mental work, behavioral manifestations, and treatment. According to her schema, the emotions of childhood trauma are terror, rage, denial, numbing, grief, shame, and guilt. The mental work includes misperceptions, distortions of time, remembrances, school and fantasy work, and repetitive dreams. The induced behaviors are revealed in play and reenactment. The range of symptoms and character disorders that she attributes to childhood trauma is virtually limitless, and so it follows that a full range of therapies is required to treat those psychopathologies. And so, in the end, we are back at the beginning, but now with a great many details.

The body of Dr. Terr's work forms a major contribution to establishing the crucial importance of real life events in the genesis of psychopathology, thereby correcting some of the effects engendered by classical psychoanalysis, which continues to downplay the importance of external reality. However, in emphasizing this point so exclusively she may have allowed the pendulum to swing a bit far in the opposite direction. Most of her clinical material allows little opportunity to discover the ways in which preexisting psychodynamics have shaped the response to the traumatic event. Her studies almost exclusively take trauma as the point of departure, and thus the presentations of clinical material sometimes seem two dimensional. Still, the reader cannot but be deeply impressed with the author's commitment and that she has made an enduring contribution to her subject. This book has the ingredients of a classic, and it might have achieved that status more securely had the author reached less broadly and more deeply.

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**Surviving Trauma: Loss, Literature, and Psychoanalysis,** *by David Aberbach. New Haven, Conn., Yale University Press, 1990, 173 pp., $22.50.*

In Hebrew there is an elegant, elusive word for which no English equivalent exists: *chesedh*. It is the highest level of mercy, empathy, and insight there is. It allows us to get inside the skin of the other, see the world with the other's view.

David Aberbach is an associate professor in the Department of Jewish Studies at McGill University. He studied literature at the University of London and Oxford and psychotherapy at the Tavistock Clinic in London. Very carefully and artfully, he weaves a tapestry from the strands of the lives of artists, philosophers, and charismatic people. He lists among those who lost a parent or parents before they were 3 years old Poe, who lost his mother and father; Pascal, who lost his mother; Burber, who lost his mother; St. John of the Cross, who lost his father; Neruda, who lost his mother; Sartre, who lost his father; Descartes, who lost his mother; Jonathan Swift, who lost his father; Tolstoy, who lost his mother; Dante, who lost his mother; Rossean, who lost his mother; and Clare, who lost his twin sister.

Aberbach also lists those who lost a parent after they were 3 years old (the oldest was 18 years old): Sister Teresa lost her mother, psychiatrist Richard Maurice Burke lost his mother and father, Bialik lost his mother, Wordsworth lost his mother, Masefield lost his mother, Darwin lost his mother, Coleridge lost his father, Keats lost his father, William Cowper lost his mother, Rimband lost his father, Spinoza lost his mother, Sylvia Plath lost her father, Nietzsche lost his father, D.H. Lawrence lost his father, Jiddu Krisnamurti lost his mother, Hitler lost his mother, and Winston Churchill lost both parents.

Humbly qualifying his generalizations and theories by saying that there may indeed be a lot of holes in his thinking, Aberbach nonetheless succeeds in establishing his credibility when he talks about the divergent routes these individuals took in the face of loss. The paradigm shifts become very clear—almost dramatically so as one patiently wades through the enormous amount of data he presents to make his case.

We are treated to a riveting explanation, for instance, of why Churchill and Hitler, who started out with the same losses, parental rejections, and fascination with violence and war; the same artistic bent (painting); both guided by instinct rather than by reason; "both inherently unstable and prone to despotism and megalomania"; both good orators who tended to dominate their listeners; both "idealized their mothers"; and "both needed an enemy," ended up at opposite ends of the ideological and military fronts.

I was spellbound by the catholicity of Aberbach's tastes and references. His sections on Krisnamurti, John Lennon, and Marilyn Monroe show a lot of insight into such divergent personalities spanning different generations.

To therapists who truly enjoy psychotherapy, this book is a must. To "scientists" bound to the biological tunnel, this book will be a bust. Alas, it will be their loss.

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**Stressors and the Adjustment Disorders,** *edited by Joseph D. Noshpitz and R. Dean Coddington. New York, N.Y, John Wiley & Sons, 1990, 660 pp., $69.95.*

Noshpitz and Coddington undertook an Herculean task to edit a volume that would deal with the universe of stressors and the adjustment disorders. This volume is an offspring of an APA Task Force on Treatments of Psychiatric Disorders, which had its own report (1). One of the goals of *Stressors and the Adjustment Disorders* is to emphasize stress and its relationship to behavior, including the adjustment disorders.

The editors state, "The present work is not a research enterprise: It is rather an attempt to make a clinical statement about the sources of stress, the forms of stress response, and the current array of treatment possibilities" (p. xiv). Another stated purpose of the book is to heighten mental health care workers' awareness of distress and to offer suggestions on how best to alleviate the pain accompanying stress-related disorders. However, the editors have difficulty accomplishing their task because the breadth of presentations offered. Their number reduces the volume to a "how to" primer, with the exception of a few chapters. In its attempt to be encyclopedic, the book by necessity reviews topics such as psychotherapy with minimal depth and insufficient development to move beyond an introductory presentation.

In addition, the concept and construct of the adjustment disorders, so clearly articulated in the introduction, are given minimal discussion. The editors admit their dilemma: "Despite the frequency with which they are diagnosed and treated, very little has been written about these disorders" (p. 535). Authors were hard to find, and the editors acknowledge, "So we offer a less than complete account of the condition and some of its variants . . . we are by no means content with this state of affairs, but until additional literature develops, we must confine ourselves to what is available" (p. 536). In a nutshell this is the problem of the volume: its title is a promise unfulfilled.

The linkage between stressors and the adjustment disorders is the very definition of this group of disorders: a maladaptation to a stressor that should remit in 6 months when either the stressor has diminished or the patient has reached a new level of adaptation and coping. However, this is also one of the most problematic diagnoses in all of *DSM-III-R*. There is no symptom profile or checklist, and no operational criteria exist to quantify the stressor or the maladaptation. In addition, although there is a "ceiling" on the diagnosis (i.e., the major disorders that do have specificied symptoms necessary to qualify for diagnosis), the "entry level" criteria are vague, not operationally defined, and leave confusion among this subthreshold disorder, the problem-level diagnoses (V codes), and normal behavior. However, this conceptual dilemma is not addressed, nor are the important contributions of Andreasen et al. (2, 3) and Fabrega et al. (4), which offer data-based studies of the adjustment disorders, discussed.

On the other hand, in the first chapter, "The Nature of Stress: Problems of Measurement," Andrew Skodol, Bruce Dohrenwend, Bruce Link, and Patrick Shrout present in great detail the dilemmas confronting stress researchers and the current impediments to reliable and valid measurement. They also carefully consider the difficulties with the assessment of stress on axis IV of *DSM-III-R*. The rationale for including in *DSM-III* an axis for assessing psychosocial stressors was to try to add predictive validity to the axis I diagnosis. It was assumed that an individual's prognosis might be better if a disorder developed from severe stress rather than after no stress or minimal stress.

Skodol et al. point out that the stress on axis IV was to be based on the clinician's judgment of the stress that a theoretically "average" person would experience under similar circumstances and not on the reaction of a particular person who might be especially vulnerable. Assessment was to include the amount of change that resulted from the stressor, the degree to which the event was desired and under the individual's control, and the summed effect of the stressors if they occurred jointly. It was assumed that the stressor would have occurred in the year preceding the development or exacerbation of the mental disorder but allowed noting and rating of stressors that occurred before that time. Each statement posed a difficulty in operationalization and posed interesting and (in some cases) unanswered theoretical questions about stress measurement. The judgment of the etiological significance of the stressor was a major problem for rating axis IV. Problems in assessment include the following: 1) *DSM-III* does not rate events which occurred but were judged not to "have been a contributor to the development or exacerbation of the current disorder." 2) Etiological judgment leads to error because the clinician often cannot know the meaning of the relationship at the time of the assessment; this meaning may become clear only over time. 3) The severity rating should "reflect the summed effect of all the psychosocial stressors that are listed." 4) Life event stressors are different from chronic stresses, such as unemployment and being a single parent, which are actually ongoing social situations.

Current stress researchers would see these two domains as quite different. *DSM-III* gave no guidelines for the second category but mainly used life event examples. Therefore, *DSM-III-R* devised separate rating scales with examples of each type of stressor for adults and for children and adolescents. Skodol et al. state that etiological significance was also clarified: 1) the development of a new mental disorder, 2) the recurrence of a previous mental disorder, or 3) the exacerbation of an already existing mental disorder—all in attempt to reduce overlooked stressors. They quote *DSM-III-R:* "When more than one stressor is present, the severity rating will generally be that of the most severe stressor . . . . In the case of multiple severe or extreme stressors, a higher rating should be considered" (pp. 8–9). "Minimal" was removed as clinically insignificant. It is unclear whether *DSM-III-R* is any better: it is based on empirical evidence, but some find it overly complex, while others predict it will confuse clinicians and inhibit research.

Skodol et al. state that to know when a particular event is stressful one needs to know several dimensions and measure them separately: 1) independence of occurrence of events, 2) desirability of changes, 3) amount of change, 4) control over the occurrence of the event, and 5) other—whether the event leads to physical exhaustion, is life threatening, or involves altruism. And these must be factored by knowing event categories called "normative ratings." Finally, Skodol et al. describe a stress-pathogenic triad: 1) fateful loss events, 2) events that exhaust the individual physically, and 3) events that are likely to disrupt social supports. This combination may approximate stress conditions of extreme situations, and the "pathogenic triad" stresses are probably more important than measuring all stresses.

This important chapter, which takes up the entire first section of the book, sets the stage and provides a basis for the papers that follow. It emphasizes the inherent defect in the diagnosis of a disorder that requires the assessment of stress and whether it is etiologically related to psychosocial outcome or malfunction. This suggested assessment is too complex for most clinicians to apply and is still being examined in a research setting.

In section two, Types of Stressors, the volume moves to specific entities and clinical applications. It takes up in a series of chapters object loss, parental divorce, illness, accidents, pain, developmental stresses, natural disasters, fire, rape and spouse beating, other forms of violence, child abuse, assault by fellow citizens, military action, prejudice and exclusion, being accused of malfeasance, new environments, loss of an ideal, and economic trauma. The common denominator through all these chapters is the issue of a stressor.

In section three the issue of vulnerability to stress is discussed. "Pathogenesis of the Adjustment Disorders: Vulnerabilities Due to Temperamental Factors" by Stella Chess and "Stress, Neuroendocrine Patterns, and Emotional Response" by James Henry are both scholarly treatises similar to the chapter on stress measurement and offer important background for understanding the vulnerability to coping.

Section four describes a collage of protective factors against stress, including ego strengths, family support, religion, peer groups, culture, and society.

Although section five deals more specifically with the adjustment disorder syndrome, it includes a chapter entitled "Adjustment Reactions: The Psychotic Syndrome" by Sherman Feinstein, Randy Kettering, and Martin Harrow. It would seem that adjustment reaction is being used here in a different manner than adjustment disorder, which by definition is not a psychotic state but most closely related to the former category of neurotic mood disorders. Thomas Webster has an important contribution on stress and retardation.

The final section, Prevention and Intervention, is again characterized by trying to cover enormous ground. Psychotherapy, interpretation, transference, group, family, individual, child, self-help, behavioral, cognitive, crisis, and pharmacotherapy are all touched on, so that one ends up with a listing and, according to the editors, "no unique treatment for the adjustment disorders" (p. 587).

In conclusion, the important topic of this volume has very uneven coverage, not uncommon in multiauthored texts. The basic issues of stress and vulnerability are "must" reading for the mental health practitioner attempting to understand stressors and adjustment disorders. The concept of adjustment disorder itself and seminal studies have not been sufficiently incorporated. The remainder of the book is an important compendium of the multitude of stressors in the universe that confront the human being, and it provides a "how to" catalog to manage the human response—both prevention and treatment—to avoid chronic disability.

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## EATING DISORDERS

**The Eating Disorders: Medical and Psychological Bases of Diagnosis and Treatment,** *edited by Barton J. Blinder, M.D., Ph.D., Barry F. Chaitin, M.D., and Renée S. Goldstein, Ph.D. New York, PMA Publishing Corp., 1988, 481 pp., $95.00.*

Judging from the number of books published each year on eating disorders, one might think that research endeavors had made giant steps toward illuminating these curious afflictions, but this is actually not so. Nonetheless, new data have been steadily accumulating as a result of new developments in investigative methods, in drug treatment, and in basic science research. This publication incorporates some of these new perspectives and thus brings us a step closer to the true nature of these disorders.

The book is dedicated to two eminent authorities, Hilde Bruch, whose writings have become classics in the field but unfortunately seem rarely read or quoted anymore, and Albert Stunkard, whose work on obesity is well acknowledged and who is cited as Dr. Blinder's mentor.

The volume consists of 43 chapters written by basic scientists, nutrition researchers, and clinicians. It is divided into three main sections. The editors attempt to cover a great deal of territory, an ambition that is both a strength and a drawback. For example, the book opens with an excellent section on basic studies in appetite regulation. Comprehensive reviews describe neurotransmitter and peptide hormone regulation of eating and appetite written by John Morley, Allan Levine, and Dean Krahn, the complexities of operationalizing the eating process written by John Blundell and Andrew Hill, two chapters on food preferences and palatability by Barbara Rolls and Marion Hetherington and by Adam Drewnoski, and an interesting treatise on the long-term history of the human diet by Glynn Isaac and Jeanne Sept that shows the tremendous variability in food consumption and that any nutritive, nontoxic substance at one time or another has served as food for Hominidae and humans. David Margules's explanatory clarity in his chapter on the different opioid receptors regulating energy conservation and expenditure, migration, hibernation, and breeding is admirable.

On the other hand, the multiauthor coverage of the clinical aspects of eating disorders leads to some duplication. Anorexia nervosa in older women, for instance, is discussed several times. The six chapters reviewing eating or appetite disturbances in affective disorders, schizophrenia, cancer, and the menstrual cycle appear disconnected from their respective syndromal psychopathology and without a clinically meaningful link to the eating disorders.

For the careful reader of the phenomenology, the question arises whether anorexia nervosa is actually an eating disorder. The papers in this book show us that the answer may hardly matter, because eating is more and more conceived as but one event in a chain of many that contribute to the body's energy conservation and expenditure. Body weight constitutes the visible counterpart of the body's energy homeostasis. In the eating disorders, other influences, such as the culture, personal taste, social expectations and attitudes, and emotional and family problems, disproportionately affect the quality, the kind, the quantity, and the circumstances of food consumption. These chapters demonstrate how far away we are from understanding the mechanisms guiding even normal eating.

A good deal of the material in the clinical section might be familiar, but the chapters are very readable and several are prepared with true diligence. An epidemiologic issue raised repeatedly is whether the clinically apparent greater prevalence of anorexia nervosa is due to an increased incidence or is an artifact resulting from an increase in the number of chronically ill patients. Leichner and Gertler document that both factors probably play a role. Meerman et al. underscore how much body image is influenced by the individual's emotional state. Even normal women, sensitive to cultural expectations, tend to overestimate their body size.

Commendably, the book includes up-to-date reviews of pica and rumination, a carefully conceptualized description of the status of eating disorders in infancy and early childhood by Joseph Woolston, and a comprehensive synthesis of the literature on childhood and prepubertal anorexia nervosa by I. Lee Gislason. I highly recommend this part to pediatricians.

The third section refers to different treatments in use for eating disorders. In practice, treatment consumes an inordinate amount of the time and energy of patients and therapists, yet the process resists description. This book reserves a mere 15% of its pages to summarize treatment. From Katherine Dixon's fine overview of group psychotherapy it becomes clear that patients with eating disorders rarely receive only one kind of treatment; most are involved in several modalities simultaneously. Here the editors take the traditional approach and assemble nutritional counselling, behavioral techniques, psychoanalytic-psychotherapeutic treatment, family therapy, pharmacotherapy, and self-help in separate chapters as if these were alternatives. Albeit expertly written, the presentations leave a gulf between information about each option and knowing how to integrate each into an effective treatment plan.

All in all, the book will be appreciated as a valuable resource by students, psychiatrists, and pediatricians interested in eating disorders. It compresses a great deal of the pertinent basic science and clinical knowledge into one volume, is amply referenced, and thus can prove helpful as a quick source of reference.

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**Males With Eating Disorders,** *edited by Arnold E. Andersen. New York, Brunner/Mazel, 1990, 288 pp., $29.95.*

Arnold Andersen is Associate Professor of Psychiatry and Behavioral Sciences and Director of the Eating and Weight Disorders Clinic of The Johns Hopkins Medical Institutions in Baltimore. Under his firm direction, a group of investigators and clinicians have been brought together to present their studies on men and boys with eating disorders.

The didactic intent is the multimodal assessment of eating disorders, focusing on the understanding of the condition as an abnormality of motivated behavior rather than a single mechanistic explanation in terms of biological, psychodynamic, or social etiology. To quote Andersen, the hypothesis he uses to describe the mechanism underlying eating disorders may be stated as follows: "Anorexia nervosa and bulimia nervosa are examples of behavior disorders, specifically disorders of motivated behavior, all of which have as their uniting feature a common, underlying mechanism of operant (instrumental) behavioral conditioning which underlies the stepwise progression of these illnesses through a characteristic and predictable set of stages. This mechanism is not further reducible to a more basic abnormality of biochemistry or neural structure, and is not understandable, on the other hand, by reference to more complex systems of integration, such as the family unit or society in general. All behavioral disorders may be best understood by reference to a specific, unifying, nonreducible, behavioral mechanism described by Skinner." Dr. Andersen goes on to use this structured approach to provide a staging of the disorders and a mechanism for interventions that he finds to be highly successful.

The sexual difference in the prevalence of eating disorders is remarkable. The rate among males is approximately 1% of that among females. This difference may be understood in terms of the female experience of fatness as inseparable from her sexuality whereas, for the male, obesity is associated with aggression.

For the male, concerns about the body shape seem to cluster around looking masculine rather than wishing to be thin. According to most researchers, there is very little difference in the illness in males and females and there is no indication that there is an enduring gender identity disturbance in the male with anorexia nervosa.

A relationship exits between anorexia nervosa and bulimia nervosa in that these syndromes may be considered points along a continuous spectrum of illness rather than separate unrelated entities. A person who goes on to become bulimic instead of anorexic is more often impulsive, feels the psychological distress of hunger more intensely, is less tolerant of continued psychological distress of any kind, and is more likely to have a personality disorder (*DSM-III-R* borderline, narcissistic, or histrionic). In anorexia nervosa, however, the sensitive, obsessional, perfectionistic, avoidant individual is more often seen (1).

Diagnostic assessment and treatment incorporate a multimodal format that is fairly well accepted in treatment programs, converging in important aspects with the addictive model. The use of the operant hypothesis seems to unite in one explanatory mechanism a better understanding of the multimodal treatment approach.

In summary, this volume contributes greatly to the literature on eating disorders. The focus on eating disorders in males enhances our understanding of the illness as a disease rather than a syndrome or symptom complex. Biological, social, and intrapsychic factors contribute to its presentation, but Andersen makes a strong case for understanding it as he presents it—a disorder of motivated behavior.

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**Bulimia Nervosa,** *by James E. Mitchell, M.D. Minneapolis, University of Minnesota Press, 1990, 168 pp., $25.00.*

In this excellent summary, Dr. Mitchell describes details of a comprehensive assessment of bulimia nervosa, including a systematic survey of symptoms of bulimic behavior, medical complications, and comorbidity problems. The chapter on medical complications and medical management is particularly cogent and likely to be useful even to clinicians experienced in treating eating disorders. The chapter describing the psychobiology of bulimia nervosa is less clear: the serotonin hypothesis of the etiology of bulimia is well described, but the hypothesis implicating norepinephrine in the genesis of bulimia is not as well explained. In the second half of the book, aspects of treatment are described with a heavy emphasis on cognitive-behavioral techniques. The final chapter, "Treatment Techniques," gives specific guidelines with step-by-step procedures for implementing psychoeducational, behavioral, and cognitive-behavioral strategies. The following steps are included: an overview of the program, meal planning, identifying bulimic behavior, commitment to change, overview of bulimia nervosa, cues and consequences, responses, restructuring thoughts, cues and chains, body image, and relapse prevention. These specific guidelines for individual or group outpatient treatment of bulimia derive from the author's extensive pioneering experiences in cognitive-behavioral techniques. The chapter on the psychopharmacology of bulimia nervosa describes the general usefulness of the antidepressants in reducing, but not eliminating, bulimic behavior. The possible usefulness of family therapy or individual insight-oriented psychotherapy is given very little attention. Throughout the book, there is variability in style and in the apparent intended audience; for example, in one section, an elementary description of placebo control subjects is given (quite suitable for a lay audience), but in another chapter, intricate details of neurotransmitter systems are provided, suitable for a very specialized biobehavioral audience.

In general, however, this is a valuable book, likely to be particularly helpful to mental health professionals planning to undertake treatment of patients with bulimia nervosa.

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## NEUROSES AND DISORDERS OF PERSONALITY

**Classification of Neurosis,** *by Peter Tyrer, M.D., M.R.C.P., F.R.C.Psych. New York, John Wiley & Sons, 195 pp., $49.50.*

This book is a terse but detailed overview of the "neuroses" that is satisfying from both the clinical and scientific point of view. Dr. Tyrer does exactly what I hoped someone would do: he reviews and discusses the background and reasons for new classifications of psychiatric disorders that exclude the term "neurosis" and presents the relevant literature about those disorders which were once called "neurotic." Dr. Tyrer also sticks his scientist-clinician neck out by clearly stating, "My viewpoint is that of a clinician . . . the concept of neurosis is a good one for clinical practice [that] when stripped of its redundant trimmings still informs and describes better than any of its replacements" (p. xii).

The entire book is exceptionally well organized and clearly written. Chapters are devoted to each of the following: panic and generalized anxiety disorders, phobic and obsessional disorders, depressive disorders, somatoform and dissociative disorders, and stress and adjustment disorders. Nearly 400 references are provided. *DSM-III-R* and *ICD-10,* chapter II, categories F00-F99, are reviewed, compared, and discussed. Case histories of each diagnostic classification are given followed by a critique of each diagnosis regarding its clarity, its overlap with other disorders, its stability based on outcome measures, and implications of the classification for treatment.

Based on his review of the literature and his clinical sensibility Dr. Tyrer makes many pithy observations that should pique the reader's interest or elicit outrage. "Panic is an important symptom but not an exceptional one, and its classification has jumbled the anxiety disorders in a way that has stimulated research but only created puzzlement in the average clinician" (p. 41). "Confusion is rife over the diagnosis of agoraphobia with panic . . . it is not a good diagnosis, and clinicians should not be allowed to suffer its contradictions for much longer" (p. 63). Discussing depressions with milder symptoms (i.e., excluding melancholia, severe depressive episode, and delusional depression), he says, "Neither pharmacological nor psychological dissection of treatment has been useful in identifying or confirming the division of anxiety and depressive disorders that remains a fundamental part of the classification of neurosis" (pp. 85–86). Regarding the classification of the somatoform and dissociative disorders, he observes that "the notion of 'unconscious purpose' has been avoided because it cannot be measured and fails all the requirements of an atheoretical descriptive system . . . the determination to keep out the unconscious is at times only achieved by linguistic tortuosity" (p. 88). "Their relegation to an atheoretical system of classification has stultified rather than enlightened their status" (p. 109).

In the concluding chapter he reviews the causes of difficulty in diagnosing the "neurotic" disorders as listed in *DSM-III-R* and *ICD-10* and presents a proposal for a diagnostic category of "general neurotic syndrome." He is modest, orderly, and thoughtful in his proposal.

This book is recommended only for experienced clinicians, graduate students, and researchers, not for medical students or undergraduates. It provides a stimulating and provocative overview of the literature of "neurosis" and the use of the concept of "neurosis" in the classification of mental disorders. It reminds clinicians to trust their experience in the day-to-day care of patients, assures us that all is not known or resolved about patients and their illnesses, and brings the focus of classification back to the patient. Psychiatry is still an exciting and evolving discipline in which our patients do not cooperate by complying with the criteria in *DSM-III-R* and *ICD-10.*

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**Obsessive-Compulsive Disorders: Theory and Management, 2nd ed.,** *by Michael A. Jenike, M.D., Lee Baer, Ph.D., and William E. Minichiello, Ed.D. Chicago, Year Book Medical Publishers, 1990, 425 pp., $45.95.*

This is the second edition of a very useful volume originally published in 1986. For this edition, the editors have updated the chapters and expanded the book from 11 chapters to 24, reflecting the burgeoning knowledge of these hitherto under-researched disorders. The book has been reorganized into four general sections: Clinical Picture; Possible Causes and Assessment; Treatment; and Patient and Clinic Management. The aim of the editors has been to create an up-to-date, accurate, and comprehensive review of obsessive-compulsive disorder and related syndromes. On all accounts, the editors have succeeded.

The editors have also succeeded in assembling a fine group of authors, expert in their respective areas of research on obsessive-compulsive disorders. Steven Rasmussen has written a comprehensive and useful chapter on the epidemiology and clinical features, Susan Swedo, Henrietta Leonard, and Judith Rapoport provide a chapter (and data from the National Institute of Mental Health) on childhood-onset obsessive-compulsive disorders, Thomas Insel and James Winslow discuss neurobiology, Wayne Goodman and Lawrence Price review rating scales, and Lewis Baxter and his colleagues contribute a chapter on neuroimaging. These selected chapters clearly show the richness of this volume.

The book is never mundane or boring. Where else could I learn about compulsive face-picking and urinary obsessions (chapter 4)? Where else could I learn about obsessive-compulsive disorders in pregnancy and childbirth (chapter 7)? More seriously, the book is not voyeuristic; it is simply comprehensive.

Treatment and management are given considerable attention. There are seven chapters describing various forms of treatments for the disorder and three chapters describing clinical management. Although many books about other disorders provide scant information about treatment other than a hackneyed recommendation to combine medication with psychotherapy, this book is very specific. Lee Baer and William Minichiello not only review behavior therapy but portray the nitty-gritty of treatment in clinical case examples. Unlike many books that fail to acknowledge that not all patients respond, Michael Jenike actually provides a chapter on predictors of treatment failure (chapter 20).

The editors include a useful appendix in which the OCD Foundation and self-help groups are described. They also provide an appendix giving patient information. Several rating scales for obsessive-compulsive disorders and related disorders are included in another appendix.

Technically, the book is of high quality. The editing is good and typographical errors and misspelling are rare. There are excellent illustrations, including some color illustrations of positron emission tomography (PET) scan findings. The tables are useful and the referencing is thorough.

This book will prove to be useful to general psychiatrists who wish to have more information on obsessive-compulsive disorder, an illness that seems to have recently come out of the closet. It will be of particular interest to those who specialize in treating these patients and in researching these conditions. I strongly recommend it.

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**The Fate of Borderline Patients: Successful Outcome and Psychiatric Practice,** *by Michael H. Stone. New York, Guilford Press, 1990, 357 pp., $36.95.*

So unusual is this book, so monumental the task undertaken, that one is constrained to search for parallels. The attempt by Hollingshead and Redlich to determine both the range of normal and the meaning of illness in the entirety of a specific population (1) comes to mind. So unusual is the author himself that I began to think about the great naturalists, like Louis Agassiz, who spent their lives describing in meticulous detail what most of us ignore.

Michael Stone, whose extensive previous work on the borderline syndrome makes him eminently qualified for this naturalistic study, has constructed a life chart for every patient treated for more than 3 months on the General Clinical Service of the New York State Psychiatric Institute between 1963 and 1976. Of the 550 such patients, Dr. Stone was able to trace 511. Stone himself reviewed each chart, spoke with the therapists involved, and contacted the former patients and/or their families. For each of these people we now know the family constellation within which their illness occurred, what it was about them that required professional attention, how they interacted with peers and therapists, the treatment strategies used, what they were like when they left the hospital, and what became of them subsequently. All of these data, assembled during a 2-year stretch of time, were then subjected to rigorous statistical analysis.

Ranging in age from 13 to 39 years (gender distribution at parity), the most common diagnostic categories were schizophrenia and schizophreniform illnesses, a variety of conditions primarily involving disorders of mood, and the borderline personality disorders for which the study was taken on. Prime among the characteristics permitting entry into this latter category were such symptoms as impulsivity, hostility, moodiness, and the tendency to form turbulent interpersonal relationships.

All of us have worked in therapy with such patients. Among these particular patients with borderline personality disorder, however, are some of the most difficult and treacherous treatment cases imaginable. All were handled by methods thought at the time to be state-of-the-art: psychoanalytic psychotherapy, psychopharmacology where indicated, family intervention where possible, group and milieu therapy on the unit itself. Central to both the therapeutic unit and the book is the theoretical system of Kernberg (2). What happened to these patients may well deserve recognition as the definitive story of this particular syndrome as it is understood in our era.

First of all, these are potentially lethal illnesses. One in 10 of the patients committed suicide, a figure held down to that level by prompt and occasionally inspired medical treatment. Factors increasing the likelihood of a morbid outcome included alcoholism, a history of parental brutality and incest, and the tendency toward feeling shame. Factors increasing the likelihood of a favorable outcome included a tendency toward the obsessional rather than the histrionic personality, a willingness to become involved with self-help groups like Alcoholics Anonymous, genius or some remarkable talent, and (at least for the women) a degree of personal attractiveness that fostered the support and interest of others despite whatever difficulties such attention may have caused in the past.

What kind of treatment was most likely to help? The admitted bias of the therapists in this study was heavily weighted in favor of psychoanalytic technique. In this system, one uses "optimal frustration" to induce the expression of hidden conflict; the overwhelming majority of patients experienced therapist silence as inappropriate and occasionally noxious. "Supportive therapy," that much maligned and often derogated set of attitudes within which the emotional comfort of the patient is valued highly, was much more often associated by the patient with favorable outcome. Stone calculates that only 14%–33% of hospitalized patients with borderline personality disorder might benefit from an "expressive" style of treatment; therapist warmth and empathy shone out everywhere as predictors of success.

We therapists have other forms of bias that masquerade as clinical intuition; Stone is merciless in his analysis of "counterintuitive results." Homosexuality, for instance, regarded with considerable societal and therapist scorn in the early years of this study, bears no relation to degree of illness or probability of cure. Therapist style and theoretical leanings aside, the patient with borderline personality disorder must at all costs be protected during the most severe periods of dysfunction because the most significant variable is time. "Given enough time," says the author, "about two out of three hospitalized patients with borderline personality disorder . . . will get better" (p. 282). Those who never abused substances improved more rapidly. The period during which suicide is of greatest concern is that between ages 20 and 30. Patients who survive into their 40s demonstrate a significant reduction in the brittleness that fostered their inclusion into the borderline personality disorder category, even though they remain always likely to respond chaotically to major life stresses.

Should you read this book? It is like no other psychiatric text you have ever seen. For reasons of personal style, Stone favors the use of initials as labels for clinical conditions (BPD, SZ, SA, etc.), and it takes a while to catch on to his conventions. The book is full of numbers, graphs, diagrams, charts, and other visual aids uncommon in our field. Just as you resign yourself to a period of arid numerology, he drops in a couple of sentences in prose so gifted one suspects he has also written a novel. And the numerous clinical vignettes are also beautifully crafted. *The Fate of Borderline Patients* is one of those rare books which are as honest as they are frustrating—it does not all come out right at the end. My own personal opinion is that Kernberg's system is nearing the end of its period of clinical utility, soon to be replaced by one more attentive to the nature of affect. But this remarkable book will make you think about the nature of the borderline syndrome. It may even change the way you treat your own patients.

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**Multiple Personality Disorder: Diagnosis, Clinical Features, and Treatment,** *by Colin A. Ross, M.D. New York, John Wiley & Sons, 1989, 369 pp., $45.00.*

This book was apparently written by Dr. Ross in order to summarize progress in the field of dissociative disorders. It seems he wishes to do this for two reasons. The first is to help the field develop by organizing the available empirical data and the second is to provide some guidance to clinicians. There is some difficulty with the first objective. The first reason is that the field has relatively little empirical support at the present time. Dr. Ross deals with this by giving his own opinions when the thin empirical data run out. We find, for example, that he believes that all multiple personality disorders are caused by early childhood trauma, that the disorder is widespread and underreported, and that all borderline personality disorder is an epiphenomenon of multiple personality disorder. He places multiple personality disorder at the top of a diagnostic hierarchy in which it also supersedes the diagnoses of eating disorders, substance abuse, depression, and panic disorder (p. 143). He admits that his ideas are at variance with most psychiatrists, psychoanalysts, psychological researchers, feminists, biological researchers, and other groups.

A second problem in Dr. Ross's objective to summarize the field is his writing style. This takes two forms. The first is that instead of giving a complete summary review of everyone's opinion or writings in an area and then synthesizing them toward his opinion, he cites where the reader can find the other opinions and then talks extensively about his own. Readers who are not already familiar with the field cannot always tell where his opinion fits into the overall scheme of work in the area. The second problem is that his writing style is, for lack of a better word, a bit dissociated. Chapters do not always flow neatly into chapters, pages do not always flow neatly into the following pages, and at times paragraphs do not flow easily in the following paragraphs. The book could have been much improved by better editing.

The book consists of three parts—A History of Multiple Personality Disorder, Diagnosis and Clinical Features of Multiple Personality Disorder, and Treatment of Multiple Personality Disorder. The first section is divided into two chapters: "The History Prior to and Including Freud" and "Freud to the Present." (Dr. Ross feels that Freud made major mistakes in this area but is still to be respected for his clinical descriptive expertise.) The second section deals with such issues as etiology, diagnostic criteria, clinical features, standardized measurement, comorbidity, and the relationship of multiple personality disorder to nonclinical dissociation. Dr. Ross's two key criteria for multiple personality disorder (although he lists others) are the existence or two or more distinct personalities that share dominance at different times. The personality that is dominant at the time determines the individual's behavior. The third section deals with treatment outcome and principles and techniques of treatment. In this section Dr. Ross takes the position that multiple personality disorder is, at best, a totally resolvable condition; the patient can eventually be returned to the community without further contact with mental health professionals. He describes the treatment as short-term therapy going on for a long period of time. Although in certain parts of the book Dr. Ross seems to disavow hypnotic techniques, his treatment descriptions seem to include them (you do not have to formally induce a trance to use hypnotic or strategic psychotherapies).

The problem with this book seems to be that it was written too early. In a few years, when the empirical evidence Dr. Ross respects has accumulated a bit more depth, this type of book would be of more interest.

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*Reprints of Book Forum reviews are not available.*

# Letters to the Editor

## Prevalence of Substance Abuse in Psychiatric Patients

Sɪʀ: Alcoholism and other forms of substance abuse are among the most common psychiatric disorders in the general population. Prevalence studies show that substance abuse occurs at rates similar to those of anxiety and affective disorders, the two other very common psychiatric disorders (1).

However, substance abuse is not easily detected. In general medicine, substance abuse occurs frequently and is frequently missed (2). Since there is such a high rate of missed diagnosis, it is useful to know how often substance abuse occurs in the patients we see. I would like to report on a survey of substance abuse in a psychiatric population.

As a resident, I did a rotation in an outpatient psychiatry department that functioned as the community mental health center for a catchment area which included a small city as well as suburban and rural areas. One of the resident's duties was to do two initial evaluations of new patients each week. The patients were assigned randomly by the intake workers. Several patients were also referred by our department's social workers for medication evaluation or by residents graduating from the program. The policy of the clinic was not to treat primary substance abuse disorders but to refer them to other community agencies.

During 6 months on this rotation, I saw a total of 78 individual patients. Because of the random nature of patient assignment, I consider this a representative sample of the patients treated in this clinic.

On reviewing these 78 patients, I found that 31 (40%) had diagnoses of substance abuse. All but one of these patients abused alcohol, although several abused other drugs as well. An additional 26 (33%) of the patients did not have substance abuse disorders but were either spouses or children of substance abusers. Again, almost all cases involved alcohol.

None of the 31 substance-abusing patients presented with a complaint of substance abuse; they initially presented with other psychiatric complaints. All of them received other psychiatric diagnoses, although substance abuse was often the primary disorder.

These findings are consistent with three previous reports. Vaillant (3) reported an outpatient community mental health center survey which found that 40% of the patients abused alcohol, although only 2% had a diagnosis of alcoholism. At a Colorado psychiatric hospital, 40% of consecutive admissions to a short-term inpatient unit were related to drug or alcohol abuse (4). The third report was from a general hospital psychiatry unit, where the Michigan Alcoholism Screening Test was administered to consecutively admitted inpatients; 42% were found to have alcoholism, although only 4% had been given that diagnosis (5).

It appears that alcohol and other substance abuse disorders are very common in general psychiatric populations. The three reports I have cited and my own observations reported here suggest a rate of approximately 40%. This raises the possibility that reports of considerably lower rates could be the result of the diagnosis going undetected. These findings highlight the need for careful screening of all psychiatric patients for substance abuse.

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## Divalproex in Posttraumatic Stress Disorder

Sɪʀ: A number of medications have been reported in research studies or in case reports to be partly effective in the treatment of posttraumatic stress disorder (PTSD). These include antidepressants, phenelzine, benzodiazepines, lithium, antipsychotics, and monoamine oxidase inhibitors (1). Although some of these reports have noted reduction of the irritability associated with PTSD (2), there has been little written about medicating patients with PTSD and intermittent explosive disorder, except for the report of Wolf et al. (3) that carbamazepine reduces their aggression. These patients are difficult to treat with drugs because of their potential for abusing medication, combining medication with alcohol, or refusing the blood tests or the diet associated with some of the medications; thus, there is a need to have alternative drug treatments available. We chose divalproex because of its ability to reduce agitation and irritability in patients with affective disorders (4). It also requires fewer blood tests during its use than lithium does. We report for the first time the successful use of divalproex in two patients with PTSD and intermittent explosive disorder without a current affective disorder.

Mr. A had been honorably discharged from the army in 1972 at the age of 19, following a year of infantry combat in Vietnam. Since that time he had been irritable and hyperalert, experienced flashbacks and intrusive thoughts of the combat he had seen, and spent much time alone in the woods. He was considered by the Veterans Administration to be 100% disabled by PTSD. There was no history of seizures or head trauma leading to unconsciousness. Alcohol and marijuana abuse occurred episodically throughout the course of his illness and was associated with physical violence against his girlfriend or other people. Violence also occurred while he was sober. Between 1984 and 1988, trials of medication were unsuccessful; they included doxepin, buspirone, thioridazine, alprazolam, and chlorpromazine. Lithium carbonate, 300 mg t.i.d., led to moderate improvement, but he refused to continue taking it because he "felt weird." Diazepam helped slightly.

In 1989 Mr. A was given divalproex, which was gradually increased to 250 mg q.i.d. For the 6 months he took divalproex he had no temper outbursts and noted a marked reduction of irritability. His total score on the Brief Psychiatric Rating Scale (5) changed from 46 before he took divalproex to 30 afterward. He refused to have his blood levels of the drug checked. On some days he took more than prescribed, complained of blurred vision and gastric upset, and stopped the medication. Then he was given carbamazepine, 200 mg t.i.d., for 2 months. The result was a reduction of symptoms similar to that seen with divalproex. However, he stopped taking it, citing blurred vision and ataxia, and was lost to follow-up. An EEG while he was taking divalproex showed no abnormalities.

Mr. B had been in infantry combat in Vietnam for a year. He described the following symptoms since his honorable discharge in 1972 at the age of 19: irritability, decreased sleep, nightmares, flashbacks, and paranoia. He had no friends and seldom spoke to anyone. Alcohol abuse was episodic, and he had many fights while intoxicated or sober. In 1986 he shot at his car and also wounded another person. There was no history of seizures or head trauma leading to unconsciousness.

Between 1986 (his first psychiatric evaluation) and 1987 he was given nortriptyline, 100 mg b.i.d., or desipramine, 150 mg h.s., but neither helped. Unlike Mr. A (who was never diagnosed as having major depression), he was twice diagnosed as having major depression with PTSD during that time. In October 1987 his diagnosis was changed to PTSD and intermittent explosive disorder without major depression, and he was started on carbamazepine, 200 mg b.i.d., without any improvement. He failed to keep subsequent appointments, during which a dose increase had been planned. In December 1987 he was started on divalproex, which was gradually increased to 500 mg t.i.d. To help with sleep, he was also given amitriptyline, 50 mg h.s. He subsequently reported a prominent decrease in irritability and improvement in mood. The improvement was maintained for 2 months, but then he ceased coming to the clinic. No EEG was done.

We are struck by the usefulness of divalproex in these two patients, particularly for irritability or aggression. We suggest that a research trial of the efficacy of divalproex in patients with PTSD and intermittent explosive disorder be undertaken. In this population, it also remains to be determined whether the success rate of the drug would be higher than that of lithium, propranolol, or carbamazepine, all of which have been reported to reduce aggression (2, 3).

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## The Obsessive Quality and Clomipramine Treatment in PTSD

SIR: In *DSM-III-R* one of the major criteria for posttraumatic stress disorder (PTSD) is that the traumatic event is persistently reexperienced. The intrusive and compelling quality of traumatic repetitions in PTSD has been described in the literature (1). Recently, it has been demonstrated that clomipramine is successful in the treatment of depression, obsessive-compulsive disorders (2), and behaviors that are undesirable but subjectively compelling, such as trichotillomania (3). On the basis of these findings, my associates and I thought it was reasonable to assume that clomipramine should improve the intrusive and compelling symptoms and the frequent coexisting depression in PTSD.

We used clomipramine to treat seven Vietnam veterans with PTSD who were inpatients. The Impact of Event Scale (4) and the Yale-Brown Obsessive Compulsive Scale (5) were used to quantify the severity of intrusions and the obsessive quality in these patients before and after clomipramine treatment. On admission, their mean±SD score on the Yale-Brown obsession subscale was 16.00±3.87 (full obsession score=20). The mean score on intrusions on the Impact of Event Scale was 18.43±2.44 (full intrusion score=21).

All of the patients were receiving clomipramine, 100–150 mg/day; these doses were reached within 5 days after the initial smaller doses. On discharge, the mean scores were 6.57±4.31 for obsessions and 12.14±6.20 for intrusions. The mean±SD number of medication days was 10.57±2.70. The correlation between the improvements in obsession and intrusion scores was 0.83 ($p<0.01$). Among the seven patients, only one failed to show improvement in his obsession and intrusion scores.

The findings in this report suggest 1) that the intrusive symptoms in PTSD are of an intense obsessive quality and 2) that these symptoms respond well to clomipramine treatment. On admission, all of the patients had severe intrusive symptoms and viewed these intrusions as uncontrollable, irresistible, extremely distressful, and severely interfering with their functioning. After clomipramine treatment, six of the seven patients showed marked improvement in their intrusive and obsessive symptoms.

Although in this report clomipramine seems promising for treatment of PTSD, the possibility of spontaneous remission and placebo effects should be considered. A large-scale, double-blind study is needed to prove the effect of clomipramine on PTSD.

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## *DSM-III-R* Criteria for Cocaine Disorders

SIR: We have been impressed by the discrepancy between our clinical observations of cocaine abusers and the *DSM-III-R* criteria for cocaine disorders. Perspiration or chills, nausea or vomiting, and tactile or visual hallucinations are listed as three of the possible signs of cocaine intoxication (305.60). Formication (the delusion of bugs under the skin) is listed as an associated feature of cocaine delusional disorder (292.11), and it is stated that this may linger for a week or more.

In our combined experience with over 300 cocaine-dependent individuals admitted for rehabilitation, none was observed to manifest or report perspiration, chills, nausea, or vomiting. Tactile hallucinations of bugs in the skin were reported by only one individual, and this perception was present only during intoxication. It did not persist after the "crash" phase. The classic text by Maier, *Der Kokainismus* (1), refers to formication (eponymously known as "Magnan's symptom") as "a relatively rare occurrence" (p. 98).

Interestingly, the *DSM-III-R* criteria for amphetamine intoxication, withdrawal, and delusional disorders are virtually identical to the corresponding cocaine diagnoses. The only difference between the two is the absence of "visual or tactile hallucinations" from the criteria for amphetamine intoxication. This omission is particularly notable because visual hallucinations have been described in the literature on naturally occurring and experimentally induced amphetamine intoxication (2). Conversely, nausea, rarely reported in cocaine abusers, is not an infrequent side effect of *d*-amphetamine and methylphenidate (3). Further, while cocaine paranoia is transient in otherwise healthy individuals, amphetamine psychoses have persisted for weeks after cessation of amphetamine use in nonpsychiatric patients (4).

In addition to the phenomenologic differences, there is evidence that the two stimulant drugs are pharmacologically distinct. Both cocaine and amphetamine block dopamine reuptake into the presynaptic terminal, but only amphetamine amplifies presynaptic dopamine release. Also, in rodents, reserpine antagonizes the effect of cocaine but not amphetamine, suggesting that different pools of dopamine are involved in mediating their respective effects. Finally, in the clinical laboratory, intravenous cocaine, but not amphetamine, interferes with the acquisition of new information, increasing error rates without affecting overall response rate (5).

It appears that the *DSM-III-R* cocaine diagnoses are based on clinical phenomena more accurately associated with amphetamine use. We suggest a reconsideration of the diagnostic criteria for cocaine use disorders—one that reflects characteristics more specific to this drug of abuse.

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## A Severe Allergic Reaction to Mianserin

SIR: Recently, Leibovitch et al. reported a case of a severe facial edema and glossitis associated with mianserin (1). We wish to report another case of cutaneous allergic reaction to mianserin.

> Ms. A, a 39-year-old woman, had had several acute psychotic episodes in the past. She was once again admitted to the psychiatric emergency ward for an acute psychotic episode. At her arrival, she was not taking any medication, either medical or psychiatric. Results of a physical examination were normal except for a major traumatic hematoma of the right thigh. Biological tests that were performed (blood count, sedimentation rate, liver tests) were within normal limits: polymorphonuclear eosinophils=$13\times10^7$/liter; AST=8 U/liter (normal <35); ALT=13 U/liter (normal <45). CT scan of the brain revealed no abnormality. The antipsychotic therapy instituted (oral chlorpromazine, 300 mg/day) allowed retrocession of the most prominent psychotic features during the first week.
>
> The persistence of depressive symptoms required the addition of 90 mg/day of mianserin. Five days later, Ms. A received hyaluronidase, 500 IU/day i.m., for treatment of the hematoma. Within 48 hours, a pruriginous maculopapular exanthema developed over her limbs and trunk. Hyaluronidase was immediately stopped. However, the eruption remained, and 5 days later, Ms. A awoke with a massive facial edema that interfered with the opening of her eyes. The edema was painless. There was neither dyspnea nor fever. At that point, her WBC count was $1230\times10^7$/liter with 8% eosinophils ($98\times10^7$/liter), and there was a slight liver cytolysis (AST=34 U/liter; ALT=56 U/liter). There was no proteinuria.
>
> Chlorpromazine and mianserin were then withdrawn, and corticotherapy (prednisone, 25 mg the first 2 days, followed by progressive reductions of 5 mg/day) was administered for 6 days. Dermatologic manifestations resumed in 72 hours.
>
> To demonstrate that mianserin was responsible for Ms. A's symptoms, we decided to perform a reintroduction trial a few days later. The patient received 60 mg of mianserin at bedtime, and 2 hours afterward severe pruritus awakened her, and a macular exanthema over her limbs and trunk was noted. She did not sleep anymore that night. Biological tests then revealed a marked increase in total WBC count ($1930\times10^7$/liter), among which 29% ($560\times10^7$/liter) were eosinophils. Hepatic cytolysis was also greater (AST=69 U/liter; ALT=125 U/liter).

This allergic reaction to mianserin was characterized by a maculopapular exanthema with voluminous facial edema associated with prominent eosinophilia and mild liver cytolysis. It can be attributed to mianserin because of the rapid reappearance of cutaneous manifestations 2 hours after the reintroduction of the drug. Mianserin is a first-choice antidepressant drug for the elderly, because it is devoid of anticholinergic and cardiotoxic effects, and for psychotic patients, because of its sedative profile. However, we must keep in mind the potentially lethal agranulocytosis, the occasional cholestatic jaundice, and the allergic effects.

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## Bruxism and Sexual Abuse

Sir: Bruxism, or the habitual clenching and grinding of the teeth, constitutes a significant source of periodontal disease and is a poorly understood disorder. Considering the relatively high incidence of this disorder (5%–20%) (1), it is surprising that it has received so little attention, particularly among psychiatrists. Although the literature is replete with references to bruxism, its pathogenesis remains unclear. Several theories of etiology have been suggested, including organic (2, 3), mechanical (3), and psychological (4).

We wish to report on bruxism among a series of five patients in our psychotherapy practices. All were women who had been the victims of incest. The perpetrators included immediate family members such as a father and more distant relatives such as a cousin. This observation seems particularly relevant, since individuals with histories of sexual abuse can develop a wide spectrum of both psychiatric and physiological signs and symptoms (5). In a review of the English-language literature, we were unable to find any references to bruxism associated with sexual abuse among women.

Although these cases represent a small, uncontrolled sample, we wish to alert clinicians to the possibility that bruxism may be associated with sexual abuse. A more comprehensive study of these phenomena would be helpful in determining their validity as well as an effective treatment. We would be interested in knowing whether our colleagues have encountered a similar association.

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## Fluoxetine in Autism

Sir: Autism is a severe childhood neuropsychiatric disorder in which many of the affected individuals have pronounced ritualistic behavior and poorly tolerate changes in routine (1). The serotonin reuptake inhibitor fluoxetine decreases obsessive thoughts and compulsive behaviors in both obsessive-compulsive disorder (2) and major depressive disorder (3). I report here on the treatment with fluoxetine of four individuals with autistic disorder (*DSM-III-R,* 299.00) who had pronounced perseverative or ritualistic behaviors. All four were Caucasian, medication free, and living at home.

Anne was a 13-year-old girl of normal intelligence who spent several hours each evening in a bedtime routine of arranging, touching, and sniffing objects. She was started and maintained on a regimen of 20 mg/day of fluoxetine for 16 months. The rituals were completely eliminated by 6 weeks.

Bob was an 11-year-old boy of normal intelligence who insisted on listening to the games of the local baseball team on the radio. When the team lost he would have severe tantrums. A long losing streak brought him to the clinic, where it was noted that he had marked hand flapping and finger flicking and poor tolerance of changes in routine. After 2 weeks of taking 20 mg/day of fluoxetine, he could listen to ballgames without having tantrums (although the team wasn't any better). There was little change in stereotypies. These improvements have continued for 16 months.

Carl was a 19-year-old patient of borderline intelligence who had marked perseveration of grooming and writing activities, frequent flapping of his arms and hands, and swaying of his head. When his perseverative behaviors were interrupted, he would have aggressive outbursts. Fluoxetine, 20 mg/day, decreased the frequency of his stereotypies and temper outbursts by about half within 4 weeks. These improvements have continued for 14 months.

Don was an 8-year-old boy of normal intelligence with marked perseveration and touching and sniffing behaviors who was referred for frequent temper outbursts. Fluoxetine, up to 30 mg/day, produced no benefit. The drug was discontinued without difficulty.

These cases suggest that fluoxetine may be useful in the management of certain problematic behaviors in autism. Three of the four patients treated with fluoxetine showed marked improvements in ritualistic behaviors or increased tolerance of changes in routine. There were variable effects on motor stereotypies. None showed improvements in language or cognitive or social functioning. None of the four had any adverse side effects or weight loss. These conclusions are tentative because of the small number of cases. It is tempting to speculate that the action of fluoxetine may be related to its effects on serotonergic abnormalities (4) in autistic individuals.

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## Treatment of Cancer Phobia With Fluoxetine

SIR: To our knowledge there has been no report on the use of fluoxetine in the treatment of hypochondriasis. We report here a case in which the patient did not respond to other forms of treatment but improved significantly with fluoxetine.

> Ms. A, a woman with three children, sought treatment at age 43 for severe "cancer phobia" that had been present since age 26 but had become incapacitating for a year. Her mind was preoccupied with ego-syntonic, intrusive fears that she or her family members might have cancer. The fears were accentuated by minor health problems or skin blemishes. If her gynecologist told her after a vaginal examination that there was no evidence of cancer, she would be relieved for only a few minutes and would soon become preoccupied with the fear that she had a brain tumor. She did not have other phobias, obsessive-compulsive symptoms, or major depression.
>
> After lack of response to 20 months of behaviorally oriented psychotherapy, Ms. A was started on a regimen of fluoxetine, 20 mg/day p.o., while the psychotherapy continued. After 6 weeks, the fluoxetine dose was increased to 20 mg b.i.d. Within 2 weeks after that, she noted significant improvement characterized by considerable lessening in the frequency, duration, and intensity of thoughts of illness. Fluoxetine was discontinued 3 months later, as she had missed her menstrual period for 3 months.
>
> A month later her menstrual period returned. However, her cancer phobia returned 2 months after she had discontinued fluoxetine. Treatment with buspirone, 10 mg t.i.d., for 7 weeks was not helpful. Three months of treatment with desipramine, 150 mg/day (blood level=135 ng/ml), also did not help and was associated with very uncomfortable side effects of abdominal bloating, dry mouth, and blurred vision. Two months after discontinuing desipramine, Ms. A was again placed on a regimen of fluoxetine, 20 mg/day, for 4 weeks, without any improvement. The dose of fluoxetine was increased to 20 mg b.i.d., and after 2 weeks the patient began noticing significant improvement, just as in the first trial. She rated herself as "much improved" and had continued to maintain this improvement at 14-month follow-up. She has had regular monthly menstrual periods while continuing to take fluoxetine.

Our patient's symptoms fit the *DSM-III-R* diagnostic criteria for hypochondriasis. Generalized anxiety disorder and obsessive-compulsive disorder are ruled out because her excessive worry was confined to fear of cancer, she did not experience her fear as senseless, and she did not try to suppress or neutralize it. However, there are similarities between obsessions and hypochondriacal preoccupations in that both are characterized by recurrent and persistent thoughts of an intrusive nature. Since serotonergic antidepressants have been found effective in the treatment of obsessive-compulsive disorder (1, 2), it is conceivable that they may also be efficacious in the treatment of hypochondriasis. The experience with this case suggests that fluoxetine deserves further exploration in the treatment of this difficult-to-treat disorder.

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## Preoccupation With Suicide in Patients Treated With Fluoxetine

SIR: Martin H. Teicher, M.D., Ph.D., and associates (1) discussed several possible explanations for the suicidal thoughts of their patients treated with fluoxetine. However, one possible explanation was not discussed. Four of their patients had features of possible limbic system dysfunction. In their case 3 (a pleomorphic clinical presentation with symptoms of depression, bulimia, agoraphobia, and dissociation), EEG was not reported for the patient. In case 4 (major depression, alcohol abuse, and borderline personality disorder), the patient experienced dissociative symptoms while taking fluoxetine. EEG was not reported for this patient. In case 5 (major depression, borderline personality disorder, and temporal lobe epilepsy), the patient was receiving carbamazepine and clonazepam. She also developed prominent dissociative symptoms while taking fluoxetine. EEG results were not given. In case 6 (bipolar disorder and multiple personality disorder), there was an "abnormal EEG." This patient was also taking carbamazepine and also experienced dissociative features while taking fluoxetine.

No indication of temporal lobe dysfunction was given in the histories of cases 1 and 2. Neither of these patients experienced dissociative symptoms while taking fluoxetine or before.

Borderline personality disorder (2), a pleomorphic clinical presentation (3), multiple personality (4), and dissociative symptoms (5) are known to be associated with limbic system dysfunction in many instances. One of the authors' patients actually had the diagnosis of temporal lobe epilepsy, and another had an abnormal EEG and was being treated with carbamazepine. There have been difficulties—not necessarily caused by fluoxetine—in the two patients with temporal lobe dysfunction that we have treated with fluoxetine. Suicidal ideation increased in a patient with temporal lobe seizures, and she began having rage attacks for the first time. The other patient, who had multiple personality disorder, tried to hang herself while in the hospital. Both of the patients had suicidal ideation prior to fluoxetine therapy.

We suggest that if fluoxetine actually causes obsessive-like, violent thoughts of suicide (and we believe this remains doubtful), they will occur in patients with some form of limbic system dysfunction. Fluoxetine may cause a paradoxical reaction in this group, since a low serotonin level has been associated with these features. Perhaps caution should be observed when prescribing fluoxetine to this group of patients until further data are obtained.

We would also like to request that Dr. Teicher and his colleagues reevaluate cases 1 and 2 to see whether any symptoms or signs of limbic system dysfunction were present.

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### Dr. Teicher and Associates Reply

SIR: Dr. Downs and colleagues raise an interesting point regarding the possibility that patients with "limbic system dysfunction" may be at increased risk of responding paradoxically to fluoxetine. We have carefully reviewed the neuropsychiatric data available on our six reported cases and find evidence of neurological abnormalities in five patients, which appears to support this hypothesis.

Case 1. This patient had an abnormal waking EEG because of occasional shifting, bitemporal, dysrhythmic sharp theta activity. On magnetic resonance imaging (MRI) she showed focal areas of increased $T_2$ signal in deep white matter of both hemispheres associated with increased signal adjacent to the ventricular system, mild in overall extent. These findings were compatible with areas of gliosis, most likely due to microvascular disease. She also showed mild diffuse atrophic changes throughout the cerebrum, more prominent in parietal lobes at the vertex, and within the vermis of the cerebellum.

Case 2. No evidence suggesting limbic system dysfunction was found, but the patient has never received EEG study.

Case 3. The patient had an abnormal EEG when taking perphenazine, which was characterized by a few bursts of higher-voltage generalized slowing (one shortly after hyperventilation). Her brain electrical activity mapping (BEAM) scan was probably abnormal because of excess frontal slowing in the eyes-open state and because of asymmetric alpha activity observed in the left temporal leads in the eyes-open state. BEAM auditory evoked response studies showed several episodes of abnormal cerebral activation localized over right posterior temporal regions. MRI study revealed that the ventricles were at the upper limits of normal, and the frontal horns were blunted. Focal bright spots, of unknown significance, were seen cortically in the plane of the frontal horns and planes of the atrium and occipital horns.

Case 4. The patient had a history of significant head trauma in childhood with brief loss of consciousness. EEG revealed an abnormal waking record with intermittent background slow activity, most prominently in temporal regions, with a certain degree of left-sided prominence. A CT scan was within normal limits.

Case 5. The patient had a history of temporal lobe epilepsy, with well-documented partial complex seizures that responded well to carbamazepine. An EEG in the interictal state was characterized by higher-voltage slowing in both temporal leads. A CT scan was within normal limits.

Case 6. The patient had an abnormal EEG characterized by lower-voltage irregular frequency activity seen anteriorly and diffusely. Theta activity was slightly excessive over posterior quadrants, with irregular bursts of generalized theta slowing bilaterally. A BEAM scan showed increased slowing over left temporal and central parietal regions and an abnormal auditory evoked response with aberrant activation of right temporal regions and the left posterior quadrant. A CT scan was abnormal, showing significant dilation of the right temporal horn of the lateral ventricle.

It is worth emphasizing that dissociation was a very prominent feature of the obsessive suicidal state experienced by at least four of these patients and that this state had a decidedly organic nature. There was a concrete, detached, vacant, confused manner in their presentation, which lacked their normal spontaneity and range of affective expression.

While we agree that limbic system dysfunction may be a significant risk factor, two points should be emphasized. First, limbic system dysfunction is often the rule rather than the exception in psychiatric patients. Present concepts of the limbic system include the hippocampus, amygdala, hypothalamus, and portions of the frontal cortex and basal ganglia (limbic striatum). Most biological theories of mood disorders or psychosis posit abnormalities of a chemical nature in one or more of these regions. If we restrict the definition of limbic system dysfunction to include only symptoms suggestive of temporal lobe epilepsy or actual electrical or anatomical abnormalities, this remains a relatively common comorbid condition. We have previously reported a high incidence of symptoms suggesting this type of limbic system dysfunction in adults who were abused either sexually or physically in childhood (1), and we have observed a very high incidence of abnormal electrophysiological studies in hospitalized children with histories of early abuse. Thus, a large segment of the psychiatric patient population may be at risk.

On the other hand, we are not certain that limbic system dysfunction is a necessary precondition. The patient in case 2 had shown no symptoms suggesting limbic system dysfunction at any time. Over the last few months he has received a careful rechallenge with fluoxetine, starting at a dose of 4 mg/day, which was advanced to 20 mg/day over 2 months. As the fluoxetine dose was increased he gradually became more depressed, and he finally began to ruminate incessantly about suicide. At that juncture the trial was stopped before his condition could worsen any further. His suicidality abated within 2 weeks, although there was no apparent change in the severity of his depression.

Overall, we thank Dr. Downs and colleagues for their interesting and potentially important comments. We also encourage these authors to delve into their possible cases more closely and, if clinically warranted, to see how these patients react when rechallenged with fluoxetine.

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### Parents' Knowledge of Children's Suicide Attempts

SIR: We read with great interest the recent article by Marcus Walker, M.D., M.P.H., and associates (1). We believe that the issue of parents' knowledge of children's suicidality is salient in the treatment of suicidal children and adolescents. Earlier research has made it apparent that parents are often unaware of the suicide attempts and suicidal ideation of their own children (2, and unpublished manuscripts by J.M. Harkavy Friedman et al., 1989, and B.D. Garfinkel, 1990).

Our data further support this finding. In a preliminary analysis of data from a clinic for depressed and/or suicidal adolescents, we have found from self-reports by adolescents and their parents that in a group of 50 adolescent suicide attempters, only 40% of the parents reported their children's attempts. Moreover, where data were available (N=42), only nine adolescent attempters (21.4%) reported that they had told someone before their first attempt, while six of 19 recidivists (31.6%) had told someone before their second attempt. Clearly, then, one reason for parental lack of awareness is that adolescents do not reveal their suicidal behavior in the majority of cases.

However, our data include one case in which the mother reported an adolescent's suicide attempt and the adolescent did not. In fact, there is such a finding in Dr. Walker and colleagues' data as well. In their "disagree" group, there was one case in which the mother reported an attempt by her son, whereas the son reported no such attempt.

This suggests that there may be important distinctions between parental "unawareness" of suicide attempts by their children and at least two other possible explanations for parent/child discrepancies in reporting. 1) In some cases the child or the parent or both deny the fact that an attempt took place, or 2) what is regarded as a suicide attempt by clinicians is not seen as such by the parent and/or child in question. To the point, we have seen cases in which both the adolescent and the parent denied the occurrence of a suicide attempt despite the fact that the adolescent was referred to us from the emergency room after an overdose of pills or wrist slashing.

In sum, we believe that parents' knowledge of their children's suicidal tendencies is highly relevant to clinical work with families in which such behavior has occurred, and that interviews with both parents and children are needed to tease out and confront discrepancies in reporting. Further, research is needed to consider the allied but distinct issues of awareness, denial, and interpretation of events.

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## Prediction of Suicide

SIR: I would like to comment on the article "Time-Related Predictors of Suicide in Major Affective Disorder" by Jan Fawcett, M.D., and associates (1). The authors showed that a discriminant function analysis in which 12 symptoms were used was strongly associated with suicide by patients with major depression within a year of their discharge from inpatient treatment. Thirteen of 14 such suicides were predicted correctly.

The authors suggested that these symptoms may be useful in "the timely identification of patients . . . in danger of suicide" (p. 1192). I would like to point out how a different slant on these data suggests other conclusions. There were 13 true positives, one false negative, 385.4 false positives, and 554.6 true negatives. This produces very high sensitivity (93%) and modest specificity (54%). The situation becomes clearer if we look at the more clinically useful calculations of predictive power. The positive predictive power is only 3.3% (13/398.4), while the negative predictive power is 99.8% (554.6/555.6). Because of the low base rate of suicide, the symptoms that are associated with suicide to a degree beyond chance turn out to be worthless in predicting who will commit suicide.

There may be reasons for investigating which symptoms are associated with suicide, but to be clinically helpful, a method of predicting would have to have an extremely low ratio of false positives to true positives, one far lower than found with these data.

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SIR: In their recent article, Dr. Fawcett and colleagues concluded that "suicidal ideation expressed to a clinician . . . [is] related to completed suicide occurring 1 year or more after assessment" (p. 1192) and is, therefore, not a short-term predictor of lethality. Because of the potentially serious ramifications of translating this conclusion into clinical practice and minimizing the weight traditionally given to the intuitively obvious contribution of suicidal ideation to short-term risk, amplification of the authors' rationale is necessary.

Of particular concern in this regard is an explanation of how they controlled for bias introduced by the universal tendency of clinicians, especially the independent professionals who were treating the patients, to intervene and provide more aggressive treatment (often hospitalization) for patients who were expressing suicidal ideation. In other words, is it not possible that patients with suicidal ideation had a lower short-term suicide rate only because such ideation resulted in their receiving more treatment within the 1-year interval than patients without suicidal ideation? If so, might not suicidal ideation be a good predictor of short-term risk?

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## Dr. Fawcett and Associates Reply

SIR: We are in complete agreement with Dr. Rifkin that our discriminant function analysis was not sufficient evidence for the usefulness of the 12 symptoms in predicting suicide. Not only was the discriminant function analysis an insufficient basis for drawing this conclusion, it is clear from our cross-validation study of later suicides that the function predicted suicide at a rate no better than chance. We cited this exploratory analysis only to illustrate how we came to examine the role of time to suicide with respect to clinical predictors.

The statement on page 1192 to which Dr. Rifkin refers pertains to the 10 symptoms that were found to predict differentially long- and short-term suicides by a completely different set of analyses; these symptoms are listed in table 2 on page 1191. The basic points are that some of the symptoms were associated with early suicides, others were associated with later suicides, and the probabilities listed in table 2 (derived from Mann-Whitney U statistics) simply reflect which symptoms are most useful for discriminating between short- and long-term suicide.

Our primary purpose in presenting the earlier discriminant function analysis was to inform the reader about how variables were selected for the later analyses and how we arrived at a cutoff of 1 year between long- and short-term suicides. Therefore, criticism of the limitations of the discriminant function analysis in no way affects the validity of the overall study. We did not and do not recommend that the handful of symptom ratings we discussed be employed as a suicide risk prediction formula to classify patients as suicidal or nonsuicidal. The major points of our article are 1) the proposal that standardized prospective studies of suicide are of much greater clinical value than other types of suicide studies for addressing the issue of suicide prediction and 2) the proposal that clinicians and researchers conceptualize clinical assessments in terms of the difference between acute and long-term risk factors.

Many investigators have shown that in trying to predict a behavior which is as infrequent in the general population as suicide is, it is inevitable that a large number of false positives and false negatives will be generated under the best of circumstances (1–3). MacKinnon and Farberow (4) demonstrated that even if one began with a suicide prediction formula that showed 99% sensitivity (something far beyond present capabilities), only 20% of suicides could be correctly predicted. We ourselves have emphasized that no one has ever demonstrated that any standardized suicide risk prediction scale can pick out persons who go on to commit suicide in samples other than the sample that generated the scale (5).

Having said this, we must take issue with a second point in Dr. Rifkin's letter, that is, the contention that symptoms able to discriminate between a 3% and a 0.2% base rate are "worthless in predicting who will commit suicide." We disagree. Assume, for example, that we have a treatment for preventing suicide that can be administered to a large number of people but not to everyone in society. To whom would we give this treatment? It probably makes sense to administer it to individuals who are at greatest risk of suicide (such as 5%–10% of an estimated 10 million patients with depression) rather than those at least risk. If we could produce a symptom profile that identified such a high-risk subgroup, we could administer the treatment to those persons who are at greatest risk.

One can also argue that improving the prediction of the probability of an individual committing suicide can eventually lead us to greater accuracy in classifying patients. If one set of variables allows us to identify 50% of our depressed population that has a much higher suicide risk, this simplifies the study of suicide because we can profitably zero in on the subgroups with the highest risk. A 3% discrimination rate is a 15-times greater improvement over the cited 0.2% base rate.

In response to Dr. Block and Dr. Behfar, we can only point out that on page 1193 in the Discussion section of our report, we stated,

> Although the outcome of this limited sample suggests that such traditional risk factors as previous history of suicide attempts and suicidal ideation were not highly predictive of short-term suicide, such factors should not be dismissed in the clinical assessment of suicide risk. Rather, these initial findings should draw attention to the following issues: 1) the importance of standardized prospective data for studies of completed suicide, 2) the importance of assessing patients in terms of acute versus long-term suicide risk, and 3) the possible value of anxiety symptoms (panic attacks, psychic anxiety, psychomotor agitation, global insomnia) as precursors of suicide and target symptoms for vigorous treatment efforts.

We are concerned not about the communicators of suicidal ideation getting more treatment but about clinicians not being sufficiently vigorous in treating depressed patients who deny suicidal ideation when clinically evaluated. Until such time as a standardized, prospective, large-sample study of suicide with the capability of documenting all intervening psychosocial and biological treatment has been reported, however, we can only speculate about whether our interpretation or that of Dr. Block and Dr. Behfar is more correct.

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## Need for Reporting of Gender Differences

Sir: We read with interest the article "Axis II Comorbidity in Substance Abusers" by Edgar P. Nace, M.D., and associates (1). We were surprised that the numbers of men and women in the study were not reported. Previous work has suggested that men and women differ in many important ways in their experiences with substances that are subject to abuse (2, 3). These differences include exposure, physiologic response, vulnerability to problems with substances, and psychological, behavioral, and genetic variables. The two sexes also differ in their expression of personality disorders and related variables.

Because of these well-documented differences between men and women, it is important to analyze men and women separately, even if the numbers of women are small. If no significant differences are found, it might be appropriate to report the results on the basis of the combined samples and to convey all of this information to the reader.

The authors did note that there were no gender differences in the proportions of men and women who had personality disorder diagnoses. However, this is not the only variable to consider when determining whether the two samples differ. For example, they did not report gender-related comparative information on type of personality disorder (considering that antisocial personality disorder is far more prevalent in men), demographic characteristics (such as age and education) that would be likely to affect the results, and gender differences in the expression of substance abuse. It would be important to the analysis to determine that men and women do not differ on all of the clinically relevant factors before lumping the two groups together. The authors showed sensitivity to the need for individualization of treatment plans to address the wide range of differences they found in their data, but this did not extend to the consideration of women as a subgroup.

We would like to suggest that the *Journal* adopt a policy of requiring published articles on clinical samples to address these concerns related to reporting on gender. This is especially pertinent for articles dealing with substance abuse, but it is also relevant for articles on personality disorder, major depression, and probably other psychiatric disorders as well.

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CAROL S. NORTH, M.D.
*St. Louis, Mo.*

### Dr. Nace and Dr. Davis Reply

SIR: In response to the inquiry of Dr. Smith and Dr. North, our sample of 100 patients included 30 women. In the personality disorder group there were 39 men and 18 women, and in the group without personality disorders there were 31 men and 12 women. Men and women in the total sample did not differ significantly in mean age or in level of education.

In regard to specific personality disorders, the breakdown is the following: paranoid, six men and one woman; antisocial, three men; borderline, 10 men and seven women; histrionic, two men and four women; narcissistic, four men; avoidant, two women; dependent, three men and one woman; obsessive-compulsive, one man and one woman; passive-aggressive, five men; self-defeating, three men and two women; not otherwise specified, two men.

Chi-square tests were done to see if there were any differences between men and women in clusters A, B, and C of the personality disorders as described in *DSM-III-R*. No significant differences were noted.

EDGAR P. NACE, M.D.
CARLOS W. DAVIS, PH.D.
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### Innovations in Use of Pharmacological Treatments

SIR: I read with interest the letter to the Editor from William W. Weddington, M.D. (1). He presented an important viewpoint regarding novel applications of previously approved medications. As he noted, both our group (2) and Gawin et al. (3) have used desipramine to treat cocaine cravings. While Dr. Weddington rightly raised a question regarding the efficacy of this mode of treatment, this point can be best resolved by further research.

Much more important, he also raised the larger question regarding development of new adaptations of pharmacological intervention. He represents a cautious position when he states, "Precautions are advised for physicians who prescribe desipramine or other as yet unproven medications . . . . In these situations one may wish to use measures similar to those used by clinical researchers testing an investigational drug." This approach, while laudable in its intent, seems to be based on an empirical view of psychopharmacological therapy. Psychotropic medication should not, however, be prescribed on an empirical basis, i.e., symptom presentation. Rather, a thorough knowledge of the biochemical indications and actions should be the basis of prescription writing. In the literature Dr. Weddington cites, desipramine was not prescribed for cocaine withdrawal craving per se. Rather, both our group (2) and Gawin et al. (3) noted changes in catecholamine activity associated with cocaine withdrawal. Since desipramine is a noradrenergic agent, it was logical to choose this antidepressant to try to reverse noradrenergic pathological changes, of which cravings were merely symptoms. Again, it is to be emphasized that the psychiatrist should focus on treatment based on underlying causes, not symptom presentation. Desipramine, for example, is posited to ameliorate a decrease in central noradrenergic tone. Whether this decrease occurs endogenously (e.g., major depression) or exogenously (e.g., cocaine abuse) seems to miss the point. Underlying causation should be the proper focus of treatment.

Installing institutional review board procedures between the clinician and the patient in cases such as treatment of cocaine abuse would seem to deprive the psychiatrist of his or her independent ability to think. The psychiatric residency has furnished us with a knowledge of underlying principles. The mere applications of these principles should not be arbitrarily subject to automatic pre-review. Independent judgment should remain the responsibility of the clinician. This tenet, of course, would not apply to new, untried medications, but only to those previously approved for prescription use by clinical physicians.

Dr. Weddington's concerns are shared by all responsible clinicians. He has conceptualized a viewpoint in the ongoing debate on the limitations of individual practice and applied it to the specific area of treating drug abusers. While I do not agree with his conclusions, I welcome this opportunity to respond.

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A. JAMES GIANNINI, M.D.
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### Dr. Weddington Replies

SIR: Dr. Giannini offers a different opinion regarding the clinical practice of prescribing a previously approved drug for a disorder in which the drug's efficacy, side effects, and adverse reactions have not been determined. He makes the point that subjecting such practice to outside review would discourage the ability of the clinician to think and do damage to clinician autonomy and independence. However, I believe that rather than inhibiting clinician creativity and promoting mindless clinical conformity, such practice encourages a clinician to really think through with peers a hypothesis that has not been conclusively tested in controlled clinical trials before he or she tests it on an uninformed patient. More important, the process offers to the patient and the clinician the safeguards, although limited, of outside review and informed consent.

While I think such caution is advisable in general medical/psychiatric practice, I feel it is particularly important in treating persons with addictive disorders, many of whom abuse prescribed drugs or may be too impaired in the early phase of recovery to comply safely with directions for taking medications, even those which are proven and approved.

WILLIAM W. WEDDINGTON, M.D.
*Chicago, Ill.*

## Comments on the Natural History of Alcohol Abuse

SIR: The retrospective analysis by Deborah S. Hasin, Ph.D., and associates of the natural history of alcohol abuse (1) is an incomplete attempt to study the longitudinal progression of alcohol consumption practices, especially the relation of early problem drinking to later, more enduring patterns of addictive drinking. Investigators have found that the distinctions between problem drinking (with adverse consequences) and addictive drinking are not at all clear, cross-sectionally or longitudinally. Schuckit et al. (2) did not find a difference between alcohol abuse and alcohol dependence according to *DSM-III* criteria in terms of alcohol-related consequences and demographic features. Fillmore (3) found that early problem drinking is significantly related to later problem drinking over a 20-year period. Vaillant (4) concluded, in his 33-year follow-up study, that asymptomatic alcohol drinking is a common outcome for many drinkers, but those with greater symptoms were limited in their ability to drink without adverse consequences over time.

Of paramount importance is that according to epidemiological studies, it takes decades of follow-up to understand that alcoholism is often a progressive disorder. Viewed over the short term, alcoholism appears extremely unstable and not progressive. The title of the study is misleading because a 4-year interval is insufficient to draw conclusions and make definitive statements about the natural history of alcoholism. Moreover, a high remission rate for alcohol abuse (70%) is just as suggestive of chronic alcoholism (5).

According to the Epidemiologic Catchment Area study, 1–5 years is the most common duration of alcohol consumption by those alcoholics who have been in remission over a year. The study by Dr. Hasin and colleagues does not refute what is already known about alcoholism: that it is a chronic remitting and relapsing disorder.

It is interesting that, indirectly, their study may support the point that "abuse" is not a useful diagnostic term. Simply, the criteria for abuse and dependence in *DSM-III-R* do not clearly distinguish two separate categories or disorders. A major purpose of a diagnostic term is to classify, distinguish, and indicate a prognosis. Abuse as a diagnosis serves none of these functions. Furthermore, abuse as a diagnosis actually detracts from the goal of medicine to serve the patient. The term "abuse" is a vernacular expression that reflects attitudes and beliefs in our society and does not represent a scientific or medical nosology. To abuse means to put to a wrong or improper use, so as to injure or damage. A synonym is "deceive." Abuse also clearly implies a willful act that arises out of a voluntary state and maintains an ethical or moral position. It also represents a retreat to *DSM-I* and *DSM-II* conceptions, where alcoholism and drug addiction were considered personality disorders. This would mean, among many implications, that alcoholism and drug addiction are not primary disorders. In a sense, the nomenclature will have come full circle if the term "abuse" is maintained as an expanded diagnostic category (6).

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NORMAN S. MILLER, M.D.
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SIR: The recent article by Dr. Hasin and colleagues provided interesting information on the natural history of alcohol abuse. However, their data only weakly support their conclusion that "alcohol abuse often has a course distinct from that of alcohol dependence." Moreover, this conclusion, if correct, does not necessarily support the inference that alcohol abuse and alcohol dependence should be considered as distinct entities. Despite the fact that the outcomes of the two groups were significantly different by statistical testing, the raw numbers are surprisingly similar; that is, 46% of the men with alcohol abuse and 39% of those with alcohol dependence were in remission at 4 years. And while 30% of the alcohol abusers had progressed to dependence over that time period, 15% of the alcohol-dependent men had crossed over into the abuse category.

These numbers suggest that there is considerable movement in both directions, from one category to the other. One could just as plausibly interpret these data as supporting a contention that abuse and dependence represent a clinical spectrum and that a given patient can move back and forth along that spectrum with the passage of time.

Two methodologic limitations of this database prevent one from drawing more specific conclusions about this back-and-forth movement. First, a more complete appreciation of the course of alcohol-related disorders would emerge from follow-up data on the initial cohort of 413 drinkers who did not have characteristics of abuse or dependence. How many of these men developed alcohol-related problems? For those who developed alcohol-related problems, were there any characteristic patterns through which these problems evolved? Second, because the subjects were identified and labeled at a single point in time (the year 1969), we have no data on how their alcohol use evolved prior to that point. For example, how many subjects who were abusers in 1969 had previously been dependent, and vice versa?

Finally, the article did not address the issue of treatment. If alcohol abuse and alcohol dependence have different susceptibilities to treatment, or if different proportions of the two groups received treatment in this study, then treatment effects (as well as natural history) might have influenced the 4-year outcomes.

We agree with the authors that there might be strong practical reasons to support a dichotomy between alcohol dependence and abuse. For example, groupings with homogeneous characteristics might facilitate research efforts and more logical application of treatment methods. But the data in this study do not provide convincing evidence either to support or to deny a deeper pathogenetic basis for such a dichotomy.

ALLAN BRETT, M.D.
LAWRENCE FRIEDMAN, M.D.
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## Dr. Hasin and Associates Reply

Sir: Our article represents the only effort at longitudinal research on the differentiation between the 1987 *DSM-III-R* definitions of alcohol abuse and alcohol dependence in an untreated sample. We agree that information on the movement into and out of abuse and dependence prior to the time periods reported would have been helpful. We can provide the information that of the initial cohort of 413 nonproblem drinkers, 8% had developed indicators of alcohol abuse at the second assessment, while another 4% showed evidence of both abuse and dependence. We note that treatment or self-help for alcohol problems (even speaking once with a doctor) was extremely rare in this sample, and thus treatment was unlikely to have had a major impact on the results.

We do not think that our findings support in any way the conclusion that alcoholism and drug addiction are personality disorders or that alcohol and drug use disorders are, by definition, of lesser importance or severity than other disorders. We agree that a 4-year interval is a short period of an individual's life and that more would be learned from a longer period of follow-up. Other limitations to the study are noted in the article itself. We did not expect that this study would provide the last word on the issue addressed. However, a clear gap in research using *DSM-III-R* criteria existed with respect to our topic. Given that research on longitudinal course represents one of the standard methods of validating diagnostic definitions, the data provided a useful preliminary means of investigating the validity of the abuse/dependence distinction. Clearly, further research on larger samples is needed, with more complete assessment of the diagnostic criteria and shifts in condition over time. We hope that this article serves to stimulate interest and research on this under-studied nosologic issue.

DEBORAH S. HASIN, PH.D.
BRIDGET GRANT, PH.D., PH.D.
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## Social Phobia and Agoraphobia in Alcoholism

Sir: The findings reported by Matt G. Kushner, M.A., and associates (1) linking social phobia and agoraphobia with alcoholism have treatment implications that should be made explicit. Many alcohol counselors, therapists, and programs equate patients' resistance to participation in Alcoholics Anonymous (AA) with poor motivation for recovery. The data presented by these authors, however, suggest that alcoholics with these phobias may find attendance at such meetings a prohibitive, anxiety-ridden ordeal. I have one patient who told me that he can handle meetings that have speakers but abhors discussion sessions where he may be called upon for comments. He remembered feeling that way as a youngster in school, too. It is important, therefore, to assess carefully the presence of these problems and recognize the role their presence can play in plans for comprehensive treatment.

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## Normal Smooth Pursuit Eye Movements in Volunteer Subjects Meeting Schizotypal Personality Disorder Criteria

Sir: Larry J. Siever, M.D., and associates (1) recently reported an abnormality in smooth pursuit eye movements, a potential trait marker of schizophrenia, in a clinical sample of *DSM-III* schizotypal personality disorder patients. These results support the hypothesis that the phenotype of schizophrenia underlies the schizotype. Alternatively, schizotypal personality disorder may be genetically distinct from schizophrenia while being phenomenologically similar. In this case, the finding of abnormal smooth pursuit eye movements in schizotypal subjects would fail to support the claim that they are a trait marker of schizophrenia, since mild schizotypal symptoms such as cognitive slippage or perceptual distortions in these subjects affect the test results. Such mild schizotypal symptoms may frequently be present in family members of schizophrenic probands or in patients themselves when they are in remission.

Schizotypal personality disorder, although highly prevalent in schizophrenic families, is not uncommon in normal families (2). The disorder in the general population may be heterogenous in its etiology, with only a subpopulation of cases related to the schizophrenic phenotype. Under such circumstances, the selection of the samples obviously influences the results of schizophrenia marker studies. This is illustrated by our study, which sampled schizotypal subjects from the community.

Subjects for our study were recruited from the community by a newspaper advertisement. Extensive structured clinical interviews (3) and a subset of the WAIS-R were given to obtain *DSM-III* axis I and axis II diagnoses and an estimate of general intellectual functioning. Of the 28 volunteers assessed, 10 had no axis I or axis II diagnosis, 11 had schizotypal personality disorder, and seven had other personality disorders (mainly borderline and antisocial). All three groups showed similar ranges of ages and estimated full-scale IQs. Smooth pursuit eye movements were recorded and scored with methods described previously (4).

The schizotypal subjects, when matched on estimated full-scale IQ, performed as well in the smooth pursuit eye movement task as the normal subjects and those with other personality disorders. The mean±SD pursuit scores in the three groups were 2.02±0.68 (schizotypal), 2.25±0.74 (normal), and 2.23±0.78 (other personality disorders).

Our results suggest that in a sample of schizotypal personality disorder subjects who are living in the community, are not identified as patients, and have a full-scale IQ comparable to that of control subjects perform normally on a pursuit eye movement task. In an earlier study (5), Dr. Siever and associates observed that poor trackers had cognitive and attentional impairments in addition to schizotypal features. Although cognitive or attentional measures were not reported in the more recent report of poor smooth pursuit in schizotypal patients, these subjects were functionally impaired, requiring treatments including hospitalization. We suggest that the smooth pursuit eye movement abnormality identifies schizotypal subjects who have a deteriorating course and/or are cognitively and functionally impaired. Whether only these schizotypal subjects have a genetic relation to schizophrenia is not clear.

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### Dr. Siever and Colleagues Reply

SIR: Dr. Thaker and associates report qualitative pursuit scores of volunteers meeting *DSM-III* criteria for schizotypal personality disorder and volunteers with other personality disorders or with no personality disorders, as determined by the Structured Interview for DSM-III Personality Diagnoses. They suggest that eye movement dysfunction is associated specifically with schizotypal personality disorder only when it is accompanied by cognitive and functional impairment, which were not present in the subjects of their study. Another, not inconsistent interpretation of the apparent discrepancy between their results and ours is that the criteria for schizotypal personality disorder are not yet sufficiently discriminating to exclude subjects in a volunteer population who have psychopathology unrelated to schizophrenia. For example, social isolation and anxiety are not uncommon in avoidant individuals, who may be more closely related biologically to those with anxiety disorders, while paranoid ideation and dissociative symptoms such as derealization and depersonalization are common in borderline personality disorder patients (1) and may be related to their underlying affective instability and impulsivity (2).

*DSM-III-R* has modified the criteria for schizotypal personality disorder in the direction of reducing these artifacts (e.g., elimination of dissociative symptoms, addition of the odd or eccentric criterion), and further refinement of these criteria has been proposed for *DSM-IV*, which might reduce the confounds of anxiety- or affective-associated psychopathology which mimic that of the schizotypal (3). Preliminary studies raise the possibility that such refinements may increase the specificity of the familial relation of schizotypal personality disorder to schizophrenia (unpublished manuscript, J.M. Silverman et al., 1990).

At one time, psychotic symptoms and severe social dysfunction were considered presumptive criteria for schizophrenia, while it is now recognized that these symptoms can also be characteristic of bipolar patients. Similarly, mild psychotic-like symptoms and social dysfunction might not be specifically related to schizophrenia, and, analogously, attention to the presence of affective symptoms in connection with these criteria might improve specificity for schizotypal personality disorder. Studies using external validators (genetic, biologic, etc.) and explicitly evaluating these possibilities are required. Furthermore, as noted in our article, studies using eye tracking measures will need to make use of specific quantitative indices to achieve better discrimination of diagnostic groups.

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### Nonpurging Bulimia Nervosa and Binge Eating Disorder

SIR: Una D. McCann, M.D., and W. Stewart Agras, M.D. (1) have reported the successful treatment of what they refer to as "nonpurging bulimia nervosa" with desipramine. Dr. Agras has recently joined a group of investigators who are conducting collaborative studies of a new eating disorder, binge eating disorder, that appears to be conceptually the same as nonpurging bulimia nervosa. The results of a multisite field trial of the diagnostic criteria for this disorder in almost 2000 subjects indicate that binge eating disorder is common among persons attending hospital-affiliated weight control programs but is relatively rare in the community. The disorder is more common in females than males and is associated with severity of obesity and a history of marked weight fluctuations.

On the basis of these results, the DSM-IV Work Group on Eating Disorders has recommended that binge eating disorder be considered for inclusion in *DSM-IV*. However, before the group can make a final decision regarding its inclusion in *DSM-IV*, additional research needs to be conducted. Investigators interested in the results of the initial field trial of the diagnostic criteria (article by R.L. Spitzer et al., submitted for publication) or in studying binge eating disorder and using assessment instruments developed by our collaborative group should contact me.

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## Dr. McCann and Dr. Agras Reply

SIR: Dr. Spitzer points to a similarity between the entity that we called "nonpurging bulimia nervosa" and binge eating disorder, an eating disorder currently being considered for inclusion in *DSM-IV*. In a study comparing purging and nonpurging bulimic subjects (1), we found the two groups to differ in several regards. Bulimic subjects who engaged in self-induced vomiting tended to be younger, reported more frequent binge eating, and were more likely to have a coexisting personality disorder. In contrast, nonpurging bulimic subjects were more likely to have histories of substance abuse and, as mentioned by Dr. Spitzer, to be overweight.

While the differences between purging and nonpurging bulimic subjects could be interpreted as evidence that the two disorders are separate, there are alternative explanations. It is possible that within the category of bulimia nervosa there is a spectrum of distinct clinical subtypes. This possibility led us to divide bulimia nervosa into purging and nonpurging subtypes. As such, differences in affective and personality features among individuals with bulimia could account for differences in expressed symptoms.

Further research is needed to understand better the relation between binge eating and bulimia nervosa. It is possible that better and more specific treatments for bulimia can be achieved if different ancillary symptoms in bulimic patients are targeted when treatment plans are designed.

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*Stanford, Calif.*

## Request for More Information About Study of Rapid Cycling in Affective Disorders

SIR: Edward A. Wolpert, M.D., Ph.D., and associates presented some interesting data in their report on rapid cycling in bipolar disorder (1). Unfortunately, some information was missing that the discriminating reader will find essential in order to interpret their data and to evaluate the conclusions they have drawn.

The authors did not mention the system of referral to their hospital, which is a very important consideration when reporting cross-sectional descriptive data. The reader has no idea whether the patients described were from the general community, a subspeciality clinic, or a research setting. In addition, there was no discussion of whether the different rates and characteristics of the bipolar patients with rapid cycling might have been related to a change in hospital admission patterns over the three decades studied. For example, clinicians are now much more aware of rapid cycling in affective disorders. In 1985 more of these difficult-to-treat patients might have been referred for inpatient assessment and psychopharmacologic treatment, whereas in 1960 these patients might have been given diagnoses of personality disorders and not referred for hospital treatment. The frequency of cycling appears to have increased, but in fact the samples were taken from different populations.

In the 25-year time span there may also have been changes in the hospital itself that would alter referral patterns, such as an increase in inpatient beds, the formation of a mood disorders subspecialty clinic or a clinical research center, or a change in the research focus of specific investigators. While the results of the study are intriguing, without this information the reader cannot be confident about the validity of the cross-sectional comparisons of the three time periods studied.

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RAYMOND W. LAM, M.D., F.R.C.P.(C)
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## Dr. Wolpert and Associates Reply

SIR: Dr. Lam raises several questions in regard to our article in which our data showed that 1) rapid cycling is not unitary, with a range of frequent or mixed-state cycling patterns evident in a number of modern-day hospitalized patients with bipolar affective disorder, 2) rapid cycling episodes occur more frequently among bipolar than unipolar patients, and 3) rapid switch processes may have become more widespread for some bipolar patients.

Dr. Lam raises two questions: in what type of hospital setting was the research conducted, and are the populations we studied in 1960, 1975, and 1985 comparable? The hospital involved, the Psychosomatic and Psychiatric Institute of Michael Reese Hospital, was described by a team of sociologists, anthropologists, and psychiatrists in 1958 (1); a follow-up was obtained in 1968 when Moos studied our five nursing units while developing his ward milieu scale (Rudolph Moos, personal communication, Dec. 12, 1968). All observers have considered the hospital's treatment emphasis to be psychoanalytic. Nevertheless, meprobamate and lithium carbonate were made available to attending and resident psychiatrists under research protocols before they were available to the general population of psychiatrists (2). As early as 1985, ECT was used for "very fast" rapid cycling (3), and as early as 1968, lithium was administered to a 5-year-old child who had had classic, adult-form manic-depressive illness from birth (4). In addition, the hospital treatment program is viewed by many as having psychiatrists with expertise in the treatment of bipolar affective disorders in general and rapid cycling in particular.

Throughout the years, 80% of the patients studied were treated by private psychiatrists and funded by private insurance or by self-payments, and 20% were treated by residents and funded by government programs or charity payments. Diagnostically, a rough balance of 40% affective disorders, 40% thought disorders, 15% personality disorders, and 5% organic disorders was maintained. The attending staff continues to exceed 150, of whom about 30 are active in hospitalizing patients. The typical resident aimed at private practice and postgraduate analytic training.

Dr. Lam's central question is, Are our three populations comparable? The answer is a qualified yes. This study was a naturalistic one, since patients were admitted according to uncontrolled referral patterns and treated by psychiatrists whose knowledge and bias changed with general developments in the field over the years. However, the institution in which the patients were treated retained its general orientation and major referral patterns intact. The populations studied were as comparable as they could be in a noncontrolled study of patients admitted to a free-standing psychiatric unit of a general medical hospital in which the private practice of psychiatry by independent practitioners is emphasized.

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EDWARD A. WOLPERT, M.D., PH.D.
MARTIN HARROW, PH.D.
JOSEPH S. GOLDBERG, M.S.
*Chicago, Ill.*

## Psychological Effects of Combat

SIR: Although I enjoyed the letter from Dennis H. Grant, M.D. (1) suggesting that combat is so abnormal an experience that it damages without fail and that we should not look for deficits in the person afflicted with posttraumatic stress disorder (PTSD) before or after the war trauma, I cannot agree with his observations. Having been one of the last Army psychiatrists to serve in Vietnam in an evacuation center, Dr. Grant certainly was exposed to a demoralized remnant of our fighting forces. Having served early in the war in a cohesive combat unit, I did not see the demoralization and later development of large numbers of "nostalgic casualties" (substance abuse, indiscipline, sexual license) that ultimately resulted in withdrawal of U.S. forces and destruction of the Republic of South Vietnam (2).

We are all prisoners of our history, not only reasonably healthy psychiatrists but also soldiers who suffer from PTSD. Studies do not support the belief that exposure to combat is always traumatic. Soldiers in cohesive units who enjoy good leadership seldom suffer from acute PTSD (combat fatigue) or chronic PTSD, particularly if they return to supportive social environments (3). Human history is replete with instances of combat and individual adaptation to conflict, perhaps making it a more normative experience overall than our recent "civilized behavior," which prevents overt expression of aggression in most instances. Chronic PTSD is truly a biopsychosocial disorder with (in individual cases) varying protective and predisposing physical and psychological elements, social and physical elements at the time of trauma, and subsequent social reinforcement of symptomatic behavior (4). It only takes observation of sky divers to realize that one person's trauma is another person's pleasure.

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## Disinhibition After Lorazepam Augmentation of Antipsychotic Medication

SIR: We read with interest the article "Efficacy of Combinations of Intramuscular Antipsychotics and Sedative-Hypnotics for Control of Psychotic Agitation" (1). However, we feel that the following cautionary note is in order.

> Ms. A was a 34-year-old woman with a 16-year history of paranoid schizophrenia. Despite medication from each of five different classes of antipsychotics, to a chlorpromazine equivalence of at least 1000 mg/day, both orally and parenterally, she remained acutely disturbed. She suffered auditory hallucinations, delusions, and agitation, pacing up and down the ward continually and shouting for the voices to stop. For sedation, she was started on a regimen of methotrimeprazine, 200 mg q.i.d., but without effect. Lorazepam, 1 mg q.i.d., was added, and a marked reduction in her agitation was noted within 2 days.
>
> Over the ensuing weeks, brief periods in which Ms. A again became distressed prompted an increase in the dose of lorazepam (a further 2–4 mg/day, p.r.n.). With this increased dose she became disinhibited. Previously, she had never been violent, but she became so, assaulting a staff member. The additional lorazepam was omitted and she returned to her former self; there were no other violent incidents. A similar sequence of events, with another assault, occurred 2 weeks later, shortly after her dose of lorazepam was again increased by 2–4 mg/day. She continued to be treated with methotrimeprazine, 200 mg q.i.d., and lorazepam, 1 mg t.i.d., and has remained well over the subsequent 8 weeks.

Paradoxical rage reactions to benzodiazepines have been well documented (2), and lorazepam may be especially liable to disinhibit aggressive behavior (3). However, Dr. Garza-Treviño and associates noted no similar adverse effects in their study. The purpose of this letter is to confirm the usefulness of lorazepam augmentation in a woman with an acutely agitated psychosis. However, we also wish to draw attention to the possibility of dose-dependent behavioral disinhibition.

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E.H. TAGHAVI
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## Dr. Garza-Treviño and Associates Reply

SIR: Dr. Little and Dr. Taghavi have raised a question and answered it. It is always possible that use of a benzodiazepine (or other sedative-hypnotic) by itself may disinhibit violent behavior in a psychotic person (1–3). In such a case, one does exactly what they eventually did: combine the sedative with an antipsychotic. In our study, the combination had other advantages as well, such as less time to control agitation, fewer side effects, and fewer injections.

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## Severe Forms of Tardive Dyskinesia

SIR: In a recent article, Ramzy Yassa, M.D., and associates (1) reported their finding that severe tardive dyskinesia occurred more in male patients 40 years of age or younger and in female patients 71 years of age or older. A smaller amount of neuroleptics and more drug-free periods were associated with moderate and severe forms of dyskinesia. Tardive dystonia was regarded as a form of severe tardive dyskinesia in this study. In fact, all of the male patients in the group with severe tardive dyskinesia had tardive dystonia, and they were much younger than those with choreoathetoid dyskinesia. However, although tardive dystonia may be a variant or subsyndrome of tardive dyskinesia, there are differences in clinical appearance, pharmacological response, and possibly pathophysiological bases (2, 3). To lump it together with the choreoathetoid type of dyskinesia in studies of epidemiology may confound the picture and add confusion to the role of potential risk factors.

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HELEN F.K. CHIU, M.R.C.PSYCH.
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## Dr. Yassa Replies

SIR: Dr. Chiu seems to indicate that patients with tardive dystonia should not be lumped together with other patients with tardive dyskinesia. We agree with her that tardive dystonia may be different in several respects from tardive dyskinesia (1–3). However, at present, most authors agree that tardive dystonia is a subtype of tardive dyskinesia (1, 3). Yagi et al. (3) suggested that when tardive dyskinesia is diagnosed in a patient, a mixed condition may exist, and both a dystonic and a dyskinetic component may be present even though the patient may manifest one subtype selectively. Thus, to date, both types—the dystonic and dyskinetic—should be considered together in any epidemiological study.

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## Factors Influencing Response to Placebo

SIR: Judith G. Rabkin, Ph.D., M.P.H., and associates (1) presented interesting findings about the effects of pill-giving on maintenance of the placebo response. However, in their discussion of reasons for placebo response they overlooked a crucial element in initiating improvement and maintaining improvement with placebos, that is, the physician's concern and involvement with the patient. I believe that a large part of a patient's improvement with placebo results from the supportive nature of his or her interaction with a doctor who takes the patient's difficulties seriously and endeavors to help.

Dr. Rabkin and associates' data indicate that this relationship is more important than the actual giving of the pill. After 10 days the patients were randomly selected to continue placebo in single-blind fashion or to be told that they had received placebo but would continue to be followed for 6 weeks. All 11 patients whose medication was discontinued at 10 days and who were well at 6 weeks remained well at 12 weeks. Of 13 patients who were told at 6 weeks that they had been receiving placebo and were discharged from the clinic, three relapsed at 8 weeks.

The numbers are small, but the difference is striking and suggests that maintenance of improvement depended on continued contact with the physician after the patients had been told that they had received placebo. The first group was given the implicit message that the psychiatrist remained interested in them despite their response to placebo, whereas the latter group may have felt that they were being discounted or rejected, since they were simultaneously told that they were receiving placebo and that they would no longer be scheduled for return visits. It is good clinical practice to follow patients for a time after their medication has been tapered and discontinued to monitor for relapse, but as these data indicate, it may also be therapeutically important for patients to maintain contact with the psychiatrist after stopping medication. It is a mistake to underestimate the power of the doctor-patient relationship and the importance of subtle cues such as the timing of termination of scheduled visits.

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SCOTT N. LURIE, M.D.
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## Neuroleptic Drugs and Dopamine Receptors

Sir: A recent letter to the Editor from Douglas W. Hoffman, M.D. (1) discussed the following assertions about neuroleptic drugs: 1) all clinically available neuroleptics block dopamine receptors, 2) treatment with neuroleptics leads to changes in dopamine content and dopamine receptors in the brain, and 3) the average clinical doses of neuroleptics correlate inversely with the affinity of the drugs for $D_2$ dopamine receptors.

The exclusivity of the $D_2$ dopamine receptor as the site of action of neuroleptics was then questioned by the writer. This is a useful point, as these drugs act variously at a number of receptors in addition to the $D_2$ dopamine receptor. Mostly, these interactions seem to be responsible for the side effects of the drugs, but some interactions, for example, at sigma receptors (1) or the recently described $D_3$ dopamine receptor (2), may contribute to antipsychotic potency.

Dr. Hoffman also questioned the correlations observed between clinical doses of neuroleptics and their affinity for $D_2$ dopamine receptors (3, 4). He pointed out that [$^3$H]haloperidol was used as the radioligand for assaying dopamine receptors in obtaining these correlations, and it is now known that [$^3$H]haloperidol will label both sigma receptors and $D_2$ dopamine receptors (5). Thus, he argued, the correlations obtained reflect sigma receptors instead of $D_2$ dopamine receptors.

It is important, however, to examine this contention in the light of the properties of the $D_2$ dopamine and sigma receptors and the experimental conditions used in obtaining the correlations. It is clear that [$^3$H]haloperidol will label both $D_2$ dopamine and sigma receptors (5), and in the caudate nucleus—the tissue used for obtaining the correlations (3, 4)—[$^3$H]haloperidol binding is likely to represent roughly equal contributions from $D_2$ dopamine and sigma sites as well as some nonspecific binding. If, however, specific [$^3$H]haloperidol binding is defined, as it was in the experiments for the correlations, using 0.1 $\mu$M (+)-butaclamol, the specific binding will represent the $D_2$ dopamine receptor contribution (5).

The correlations were, however, obtained in competition experiments, and the competition for this specific [$^3$H]haloperidol binding will reflect the receptor site for which the competitor has the higher affinity. Examination of the published data (3–5) shows that the competitors used have either rather similar affinities for $D_2$ dopamine and sigma sites (haloperidol, fluphenazine, molindone) or much higher affinities for $D_2$ receptors (spiperone, clozapine, thioridazine, thiothixene). In either case, the affinities seen in the competition experiments will be reasonable approximations of the real affinities for the $D_2$ dopamine receptor. Therefore, the correlations with clinical drug doses do reflect interactions of the neuroleptic drugs at the $D_2$ dopamine receptor.

This is not to say that $D_2$ dopamine receptor blockade is the only means for achieving antipsychotic action. It will be of great interest, for example, to examine correlations between clinical drug doses and the affinities of drugs at the $D_3$ dopamine receptor (2).

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## Dr. Hoffman Replies

Sir: It was the thrust of my argument that the original reports of the correlation of $D_2$ receptor binding and clinically effective doses of neuroleptics could apply equally well to sigma receptor affinities of these drugs. Dr. Strange, in the last sentence of his third paragraph, is perhaps making more of my argument than I chose to. Further, the differences between (196)- and (+)-butaclamol are not so absolute as Dr. Strange would represent them to be, and this pair of drugs was not used in all of the original experiments on which these assumptions are based, as is alluded to in Dr. Strange's fifth paragraph.

DOUGLAS W. HOFFMAN, PH.D.
*Hanover, N.H.*

## Bupropion, ECT, and Dopaminergic Overdrive

Sir: Reminding us that the effects, both therapeutic and adverse, of new treatments may not be fully apparent until some time after widespread use, Israel Liberzon, M.D., and colleagues (1) recently described their unfortunate experience with bupropion in an older man with parkinsonism and delusional depression. Delirium developed within 3 days of the introduction of modest doses of bupropion to an ongoing regimen of amantadine, haloperidol, and benztropine; it cleared with the discontinuation of bupropion. The authors speculated that a pharmacodynamic interaction between bupropion and amantadine, resulting in "dopaminergic overdrive," promoted delirium in this patient.

While we are aware of the potential deleterious clinical implications of bupropion's actions on dopamine systems (2), we would like to add another possible factor in this case that was not mentioned in the authors' otherwise thorough discussion: the (successful) course of ECT that preceded (by an unspecified interval) the initiation of bupropion treatment. A growing body of preclinical and clinical data suggests dopaminergic effects of chronic electroconvulsive shock in rat models and ECT in patients with depression and/or Parkinson's disease. Building upon an earlier database showing that repeated electroconvulsive shock enhances dopamine-mediated locomotor behaviors, more recent animal studies have documented increases in the number (3) and function of dopamine $D_1$ receptors (with enhanced basal release of dopamine) in several brain regions, including the striatum, following chronic electroconvulsive shock. In our ongoing clinical studies at the National Institute of Mental Health (4), we are observing a mean 30% rise from medication-free baseline in CSF concentrations of the principal dopamine metabolite homovanillic acid following completion of a course of ECT. Finally, in an experimental paradigm probably closest to the clinical situation reported by Dr. Liberzon and associates, Balldin et al. (5) demonstrated increased postsynaptic dopamine receptor sensitivity after ECT, as gauged by prolactin suppression in response to intravenous challenges of the nonspecific dopamine agonist apomorphine in samples of both depressed and parkinsonian patients.

Thus, the dopaminergic synergism of bupropion and amantadine described by Dr. Liberzon and associates may have exerted the unusual potency seen in their patient because of an already (post-ECT) potentiated dopaminergic substrate, with driven transmitter output as well as heightened receptor responsiveness. The threshold for adverse effects, e.g., delirium, was thus lowered.

The relation of the reported dopamine system changes to either the antidepressant/antipsychotic or antiparkinsonian effect of ECT remains speculative (4). We endorse the caution advised by Dr. Liberzon and colleagues in the concurrent use of bupropion and dopamine agonists, and we recommend that ECT be included among the latter.

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WILLIAM Z. POTTER, M.D., PH.D.
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## Dr. DeQuardo and Associates Reply

Sir: We appreciate the opportunity to respond to Dr. Rudorfer and associates. We reported the case of a 76-year-old man with delusional depression and parkinsonism who developed delirium 2 days after receiving ECT and approximately 72 hours after bupropion, 75 mg b.i.d. (cumulative dose=450 mg), was added to his regimen of amantadine (100 mg t.i.d.), haloperidol (2 mg h.s.), and benztropine (2 mg h.s.) for prophylaxis against recurrence of depression. Prior to this he had responded well, in terms of both the mood disorder and the parkinsonism, to seven bilateral ECTs. We suggested that delirium may have been the result of dopaminergic overdrive associated with the combination of bupropion and amantadine.

Dr. Rudorfer and his colleagues suggest that dopaminergic activity may have been further increased by the patient's recent ECT. They base this assertion on their work demonstrating increased CSF homovanillic acid levels in 12 endogenously depressed patients 7 days after completing a course of ECT, as well as previous work suggesting increased $D_1$ receptor number and function and increased postsynaptic dopamine receptor sensitivity after ECT. However, enhanced dopaminergic function after a course of ECT has not been demonstrated in previous studies (1, 2). Nonetheless, the finding of Dr. Rudorfer and associates is consistent with the time course of development of delirium in our case. Enhanced dopaminergic function after ECT is also congruent with the improvement in parkinsonism seen in our patient.

We continue to advise caution in the combined use of bupropion and dopaminergic agents. This warning may need to be extended to include recent treatment with ECT as well.

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ISRAEL LIBERZON, M.D.
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## Trauma in Childhood

Sir: The report by Lenore C. Terr, M.D., on childhood traumas (1) calls for comment. For 40 years all pathology has been blamed on either mother, society, or some traumatic event. Animal breeders have always known that basic temperamental traits are genetically transmitted and determine the organism's response to stress or trauma. Dr. Terr postulates that a trauma or traumas produce certain lasting changes in the child which manifest themselves as symptoms. Another dimension must be added. The child's temperamental traits will influence the child's reaction. Concentration camp living produced lasting pathology in many children, but the majority have done surprisingly well.

Another important dimension in the study of traumatic experiences has to do with memories. The most common reaction is repression, with a gradual return of memory over varying lengths time. Psychiatry has judged this as pathological, with intervention aimed at bringing memories into consciousness. The treatment of battle casualties in World War II was based on this belief. The unfortunate results of this therapy led the military to abandon this form of treatment. The repression of painful memories may be the most successful method of dealing with such traumas (2). Let us not go against nature until we are certain that we can produce a better outcome.

The temperamental traits present before the trauma must be accounted for, and the possible benefit or change from the suppression of painful memories is not known and should not be interfered with until we know more.

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HANS R. HUESSY, M.D.
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## Dr. Terr Replies

Sir: Dr. Huessy points out correctly that there are many factors—genetic, constitutional, internal, and external—that lead to various personality traits and psychological changes in children. Focusing, as I do, upon one single factor, i.e., childhood trauma, does not constitute "blaming," however. Along these same lines, repression is not bad or good. Living through traumatic childhood events does not have to be classified as normal or disordered. I wrote the article as a clinical digest of the entire gamut of externally derived traits, defenses, and problems (normal and abnormal) that follow traumatized children into adult life. I do not intend to cast value judgments on any of these.

LENORE TERR, M.D.
*San Francisco, Calif.*

## Behavioral Disorders in Animals

Sir: I was extremely pleased to note the letter from Judith L. Rapoport, M.D., about her success with a naturalistic animal model of psychiatric disorder (1). I am a veterinarian interested in animal behavior and am also Board-certified in human psychiatry.

Animal studies are a most important area from which we can learn a great deal. For example, why do not other animals, with the exception of the harvester ant, wage war, even though they can cooperate in other respects?

More specifically, the repetitive paw-licking compulsive syndrome Dr. Rapoport described as responding to clomipramine is a good example of the proper use of the buzzword "biopsychosocial." This behavior is most likely to be found in certain genetic breeds and in certain personality types—often inhibited or introverted, often with neglectful or overattentive owners, and often in animals restricted to confined quarters with inadequate exercise.

To answer Dr. Rapoport's request, I know of only a few psychiatrists who are knowledgeable in this area. However, I suggest that she contact veterinarians, many of whom have long treated habit and behavioral problems with whatever medication and/or corrective methods were available at the time. In my memory, this goes as far back as the consecutive use of triple bromides and barbiturates to phenothiazine and the benzodiapezines. The use of hormones and hormonal manipulation is very common in veterinary medicine and even extends to castration and spaying (oophorectomy).

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IRWIN ROTHMAN, V.M.D., D.O., M.D.
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## Dr. Rapoport Replies

Sir: I agree entirely with Dr. Rothman's comments that naturalistic studies of animals are of considerable interest for psychiatry and have been insufficiently studied.

A gratifying number (over 50) of veterinarians and/or psychiatrists responded to my letter, adding considerably to my knowledge about psychopharmacological practice in veterinary medicine and the efficacy of other biological treatment (e.g., electroshock) in behaviorally disabled animals.

As a result of this exchange, collaborative studies have been initiated. I am impressed with both the collegiality and sophistication of the veterinary community.

JUDITH L. RAPOPORT, M.D.
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## Cortical Glucose Metabolism and Clinical Depression

Sir: I was interested to read the article by Jean-Luc Martinot, M.D., and associates on cortical glucose metabolism and clinical depression (1). The authors described a statistically significant association between a left-right asymmetry in prefrontal glucose metabolism and the clinical state of major depression. However, in order to appreciate the practical significance of their findings, some further clarification of their results may be necessary.

First, the key difference between their 10 patients when depressed and 10 nondepressed control subjects and the same depressed patients following treatment was a higher mean±SD right-left ratio of prefrontal metabolism (1.02±0.03) among the depressed patients than among the other two groups (0.99±0.01 and 0.99±0.03, respectively). While the authors found a statistically significant difference between these ratios by using parametric statistics, the actual difference represents only a 3% change in ratio. Between the depressed and recovered state, the mean absolute increase in prefrontal glucose metabolism of the patients was approximately 4% in the right hemisphere and 7% in the left, a relatively small difference. Given the small sample size and the modest change in ratio, it would be reassuring to know whether an equivalent nonparametric statistical test would also show a significant difference.

Second, it would be helpful if the authors could give an idea of how meaningful a right-left ratio change of 3% in prefrontal metabolism is. For example, is a difference of this degree observable when one is visually comparing reconstructed images of depressed and nondepressed patients?

Third, the authors presented data that suggest a relative hypermetabolism in striatal regions of the patients when in the depressed state compared with the control subjects and the patients when in the nondepressed state (mean±SD normalized rates, 1.15±0.16, 1.09±0.08, and 1.09±0.12, respectively). This difference is on the order of 5% and is in the opposite direction from and of a greater magnitude than that described for prefrontal areas. However, it is not statistically significant, presumably because of the greater variability in striatal regional metabolism. (The reason for this greater variability in striatal regions than in the cortex is not explained in the article, but presumably it is due to difficulties in defining striatal structures precisely.) The authors offered no comment on the striatal findings, which is unfortunate considering previous reports (2) of caudate hypometabolism in major depression. Furthermore, it would have been interesting to know whether right-left asymmetry in striatal regions was associated with depression in this sample.

Finally, although the authors looked for correlations between left prefrontal glucose metabolism and clinical scores of depression, an alternative procedure might have been to examine the correlations between change in depression scores and change in metabolism or asymmetry ratio from the depressed to the nondepressed state in prefrontal, striatal, and other regions of interest.

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PHILIP L.P. MORRIS, M.B.B.S., PH.D., F.R.A.N.Z.C.P.
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## Dr. Martinot and Associates Reply

SIR: We are most grateful to Dr. Morris for his attention to our article, and we are pleased to answer with information regarding our results. First, the reduction in right-left ratio of prefrontal cortex metabolism in the depressed patients which we found to be significant with a paired t test remained significant with a nonparametric Wilcoxon signed-ranks test (N=10, p=0.04). Second, this difference is not as small as it seems. In patients, it is about six times larger than the intrasubject variability and was observable on reconstructed images.

Third, as pointed out by Dr. Morris, the difference found in the striatal regions was larger but much more variable, which explains its nonsignificance, for the reason invoked by Dr. Morris (the small size of the striatal regions with respect to the axial resolution of our camera). We feel that it is hard to draw any conclusion from this absence of difference. As for a hypothetic striatal right-left asymmetry, we found no asymmetry either before treatment (p=0.48) or after (p=0.69).

Fourth, we agree with Dr. Morris that correlations between clinical depression ratings and metabolism would be extremely interesting. However, due to the small sample size, it would be unwise to multiply the number of statistical tests because of a higher risk of type I error.

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## Cyclothymic Mood Swings in Major and Minor Psychiatric Disorders

SIR: The findings of Christopher G. Fichtner, M.D., and associates (1) on the similar prevalence of cyclothymic symptoms at follow-up in 38 unipolar depressed, 27 bipolar, 27 other "nonpsychotic, nonaffective," and 35 schizophrenic patients are surprising. There are four points in this article that are problematic.

1. The authors' method of assessing cyclothymia is supersensitive: it not only detects the behavioral manifestations of cyclothymia (pure cyclothymia) but detects persons with only subjective feelings of mood swings (pseudocyclothymia). This latter group is not a part of the cyclothymic-bipolar spectrum (2).

2. The high rate of cyclothymia (61% in their 38 unipolar depressed patients) deserves further attention. The authors did not mention how many unipolar depressed patients had had their first or second depressive episode. The mean age was not mentioned separately for the four diagnostic subgroups, but the total sample of patients was quite young, with a very small standard deviation (23.1±3.6 years). Since for two-thirds of bipolar depressed patients the first episode is depressive (3), and many young patients (particularly those who are retarded, obsessional, or psychotic) with a first major depressive episode are not unipolar (3), a relevant proportion of the authors' 38 unipolar depressed patients might have been having the first or second depressive episode of their bipolar disorder. In this case, the high frequency of cyclothymia in the authors' "unipolar" patients at follow-up reflects the original bipolarity rather than psychopathology in general. Dr. Fichtner and colleagues mentioned only that 14 (47%) of a subset of 30 of the unipolar patients had experienced a major affective episode during the last year of the follow-up, but they did not specify the polarity of these episodes. How many patients had become bipolar I or bipolar II at follow-up?

3. To consider their 27 other psychiatric patients (six with borderline personality, four with anorexia or bulimia, etc.) as having "nonpsychotic, nonaffective" disorders may be a mistake. There is scientific evidence that these conditions are genetically, biologically related to primary affective illness, and a relevant part of such patients show full-blown depressive and/or (hypo)manic episodes during the further course of their illness (4–6). Considering this, it is not surprising that five (33%) of a subset of 15 of the "nonaffective" patients showed major affective episodes (depression and/or mania) during the last year of the 2–6-year follow-up period, supporting the findings (4–6) on the underlying unipolar and bipolar diathesis of this population.

4. Fourteen (45%) of a subset of 31 of the schizophrenic patients had experienced major affective episodes (32% depression only, and 13% both depression and mania) in the last year of the follow-up period. This surprisingly high rate calls into question the validity of the original diagnosis, particularly since the mean age of the total sample was 23.1 years, and the majority (77%) of the patients had had their first or second hospital admissions. What percentage of the authors' schizophrenic patients showed schizophrenic relapse during the follow-up? Upon observing major depressive, and particularly depressive and manic, "relapses" in young schizophrenic patients after their first or second hospital discharge, the first duty is to revise the original diagnosis (to exclude the possibility of the misdiagnosis of psychotic major depression, psychotic mania, and schizoaffective illness as schizophrenia) rather than to publish these findings as new results.

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ZOLTÁN RIHMER, M.D.
*Budapest, Hungary*

## Dr. Fichtner and Colleagues Reply

SIR: Dr. Rihmer raises several interesting questions about our study of cyclothymic symptoms. First, as we have noted, our assessment of cyclothymia was highly sensitive, targeted at periodic mood swings not necessarily accompanied by prominent neurovegetative signs. Our sample of cyclothymic patients included many who might be classified as "pseudocyclothymic" by the criteria of Akiskal et al. (1). A major issue concerns the scope of the continuum between subaffective mood swings and major affective disorders (1, 2). It is not known whether cyclothymic syndromes resembling major affective disorder are closely related to mood swings not meeting diagnostic criteria for a cyclothymic disorder (1, 2). Our findings indicate that mood swings may be significant, in that they are associated with poorer psychosocial functioning, as well as other aspects of psychopathology, in a broad range of patients.

Second, Dr. Rihmer questions whether our unipolar depressed patients included many early manic-depressive patients whose bipolar illness had not been manifest at follow-up. We have studied this question in our sample through 10 years of follow-up and found that only a minority (under 15%) of patients initially diagnosed as having unipolar depression develop a subsequent bipolar course. Whereas manic-depressive patients often present initially with major depressive and/or dysthymic phenomenology, our follow-up data are consistent with expectations, given the relatively low prevalence of bipolar disorder in comparison with unipolar depression.

Third, Dr. Rihmer points out that the concept of an affective spectrum of illness may apply to patients in our nonpsychotic, nonaffective group. This is possible for a percentage of these patients, some of whom developed subsequent major affective episodes. However, even when patients with major affective syndromes were excluded from the overall sample, a trend toward poorer functioning associated with subaffective mood swings remained. This may reflect an affective spectrum diathesis or, possibly, other factors influencing mood and vulnerability to psychopathology.

Fourth, Dr. Rihmer questions whether a percentage of our schizophrenic patients might more appropriately have been rediagnosed as having psychotic depression, psychotic mania, or schizoaffective illness. Our research suggests that such a revision is not appropriate for most of these patients. Schizophrenic patients may develop depression for various reasons (3, 4), including neuroleptic side effects (4). Very few (under 15%) of our schizophrenic patients had developed mania at follow-up. Support for their original diagnosis includes follow-up data showing a characteristic schizophrenic course involving intermittent or prolonged psychosis and poor overall functioning. Even so, one of our most interesting findings was that schizophrenic patients with mood disturbances showed more psychosocial impairment than those without. This leads us to question whether some types of affective disruption, or factors associated with it, may be an additional debilitating factor in schizophrenia. In the light of prior research on affective symptoms and schizophrenia, this issue appears to warrant further investigation.

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CHRISTOPHER G. FICHTNER, M.D.
LINDA S. GROSSMAN, PH.D.
MARTIN HARROW, PH.D.
JOSEPH F. GOLDBERG, M.S.
*Chicago, Ill.*

## Hypnotizability and Dissociation

Sir: Fred H. Frankel, M.B., Ch.B., D.P.M., in his admirable article "Hypnotizability and Dissociation" (1), invites his readers to refrain from accepting too readily the perspective that dissociation, like hypnotizability, "lies along a continuum." He thereby implicitly urges us to return to the narrow concepts of Pierre Janet, the first serious student of dissociative phenomena, in preference to the broader definitions of Bernheim, which were accepted by most contemporary authors. Unfortunately, Dr. Frankel's quote which purports to show that Janet warned against attaching too much importance to "disaggregation" (dissociation) does not accurately reflect Janet's views, and it does not appear in the reference provided. For Janet, dissociation and narrowing of consciousness were at the core of hysteria. Dissociation was defined as the separation of memories and functions from ordinary consciousness (usually in response to traumatic experiences) and their continued manifestations in the form of somatic expressions, visual images, dream disturbances, and behavioral reenactments, relatively independent of conscious control and awareness. Janet viewed amnesia, rather than suggestibility, as the fundamental issue in patients with hysteria, although he recognized that dissociation resulted in enhanced suggestibility (2, 3). He thought that the reemergence of dissociated material occurs along lines of what we would today call state-dependent learning. This is quite different from Freud's later concept of repression, although Breuer and Freud's initial formulations were derived from and similar to Janet's work (4, 5).

Janet wrote that hypnotically induced trances are controlled iatrogenic conditions with amnestic barriers similar to dissociative states. Hypnosis can both facilitate retrieval of ordinary memories and help gain access to dissociated emotional states such as traumatic memories (2, 3).

We agree with Dr. Frankel's call for precise definitions of terms and careful investigations. We hope that these, coupled with developments in understanding the nature of memory processes, can move us beyond the century-old observations of Janet.

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ONNO VAN DER HART, PH.D.
*Utrecht, The Netherlands*
BESSEL VAN DER KOLK, M.D.
*Boston, Mass.*

## Dr. Frankel Replies

Sir: The affirming comments on my article by informed colleagues such as Dr. van der Hart and Dr. van der Kolk are much appreciated. I believe, however, that they have misread the citations to my reference list.

Janet's comments on the plasticity of *somnambules* who "always confirm our own ideas" can be found on pages 136 and 137 in the 1889 edition of *L'Automatisme Psychologique* (reference number 5 in my article). The comment in the sentence preceding that quotation in my article, concerning Janet's warning to his readers not to make too much of his notion of "disaggregation," was nowhere referenced in the text of my article, nor was its source placed in the reference list.

Janet on more than one occasion recorded his concern that the importance of his ideas had been exaggerated. I will refer my esteemed colleagues to but one such reference in his *Psychological Healing*, volume I (1). Claiming authorship in 1889 of the idea that there is a modification of awareness in hysteria, and that this "subconsciousness [is] due to psychological disaggregation" (pp. 595–596), Janet then stated (p. 672), "And I have sometimes been rather rueful while watching the development of the idea, while watching its undue success." Further along in the text on page 672 he stated,

> I do not think that the subconscious is worthy of so much honour, and I believe that a single precaution will enable us to confine it to its proper role. A psychological phenomenon which is always in reality a particular form of the subject's behavior, must invariably be something which an observer can detect. What we have to shun is the subconscious which we never see, and which we can only construct imaginatively . . . .The exaggerations which have discredited admirable studies must put us upon our guard against the hasty interpretations of those who are too ready to base their conclusions upon psychological notions which are still extremely tenuous.

I believe my comment that Janet warned his readers not to make too much of the notion of disaggregation does indeed accurately reflect his views.

REFERENCE

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FRED H. FRANKEL, M.B., CH.B., D.P.M.
*Boston, Mass.*

### Dissociative Disorders and Complex Partial Seizures

SIR: The article by James A. Chu, M.D., and Diana L. Dill, Ed.D. (1) on the relation between childhood abuse and dissociative symptoms and their significant prevalence in a psychiatric population is a solid contribution to a growing area of needed clinical awareness. In this connection, I have found clinical manifestations of complex partial seizures in several psychiatric patients with histories of abuse, especially when sexual abuse was involved. Most of these were later confirmed by EEG and/or trials of anticonvulsant medication. As a consequence, I have learned that in assessing abused patients, it is necessary to rule out not only posttraumatic stress disorder (PTSD) and dissociation but also this seizure disorder.

A recent study of a small population (2) found that sexually abused female borderline patients had a high occurrence of documented or suspected complex partial seizures. Surprisingly, in that same study, the patients with physical abuse only did not show this epileptic disorder. The authors suggested that in sexually abused patients with no known head trauma, the etiology may possibly be found in the hypothetical "kindling" of alterations in the limbic system. If this suggestion proves correct, psychic seizures, like PTSD, would in some cases have their origin in a psychological trauma of a specific type. This seizure disorder, either ictally or interictally, manifests many of the symptoms mentioned by Dr. Chu and Dr. Dill as characteristics of dissociation, namely, depersonalization, derealization, amnesia, auditory hallucinations, and psychosis-like experiences. Furthermore, these limbic seizures are often difficult to differentiate from dissociative behavior (3, pp. 1037–1038). Consequently, unless these seizures were indeed ruled out by Dr. Chu and Dr. Dill, some of their cases may have involved psychomotor seizures instead of or concurrent with dissociative phenomena.

Dissociative reactions and psychic seizure episodes have similar traumatic etiologies and clinical manifestations, but their internal mechanisms and therapeutic requirements are markedly different. Untreated seizures can complicate the psychotherapy of dissociative disorders. Since the treatment of these seizures is quite different from that of dissociation, requiring anticonvulsive medication, differential diagnosis is imperative.

Speaking in general, the frequent confusion of this seizure disorder with psychiatric illnesses, the resulting treatment failures, and repeated reentries of such patients into the mental health care system have been noted in the literature (4), as has the lack of a specific diagnostic category in *DSM-III-R* (3). The inclusion of accurate diagnostic criteria for PTSD in *DSM-III* led to increased identification and treatment of that syndrome. Clear diagnostic criteria for complex partial seizures in *DSM-IV* would, no doubt, facilitate the recognition of this underdiagnosed disorder.

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WAYNE H. PETERSON, PH.D.
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### Dr. Chu Replies

SIR: Dr. Peterson's comments concerning our finding of high levels of dissociative symptoms in psychiatric inpatients with histories of childhood abuse are quite interesting. There have been a number of reports in the literature of complex partial seizures in patients who were abused in childhood. However, there has been considerable debate as to whether all these patients actually had complex partial seizures. For example, in our article we reported, "Only three of seven patients had EEG abnormalities sufficient to corroborate the treatment team's clinical impression" of complex partial seizures (p. 215). There have also been reports of a number of patients with complex partial seizures having multiple personality disorder, but there is considerable question as to whether these patients actually had classic multiple personality disorder (1).

There seem to be both quantitative and qualitative differences in the nature of dissociative symptoms in patients who have organic disorders and those who have psychogenic disorders. Our clinical experience has suggested that patients with temporal lobe dysfunction have generally milder dissociative symptoms, as well as relatively less amnesia. Our clinical observations are supported by three independent investigations (1–3) using the Dissociative Experiences Scale (4), which we also used in our study. All three studies compared scores on this scale of patients who had dissociative disorders with scores of patients who had complex partial seizures. The scores of the patients with complex partial seizures were generally only slightly above normal levels, as opposed to the highly elevated scores of the patients with dissociative disorders. For example, in Loewenstein and Putnam's study (2), the median Dissociative Experiences Scale score was 6.8 for patients with complex partial seizures, 28.75 for patients with posttraumatic stress disorder, and 47.5 for multiple personality patients, as compared to the previously established median score of 4.3 for normal subjects (4). The modest elevation in the scores of the patients with complex partial seizures was due primarily to elevation of the score on the depersonalization/derealization subscale and not due to amnesia.

The actual prevalence of patients with dissociative symptoms and childhood abuse who have neuropsychiatric disorders is still unknown but is currently being actively investigated by us. At this time the findings strongly suggest that patients who have a high level of dissociative symptoms, as determined by a high score on the Dissociative Experiences Scale, are likely to have a psychogenic dissociative disorder rather than complex partial seizures. However, given the overlap in symptoms of patients with complex partial seizures, it would seem prudent for patients who present with dissociative symptoms to undergo a comprehensive neurologic evaluation.

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JAMES A. CHU, M.D.
*Belmont, Mass.*

## Computerized Literature Searches

SIR: We read with great disappointment the article by Joseph C. Bareta, M.S., and associates (1) comparing manual and Medical Literature Analysis and Retrieval System (MEDLARS) reviews of the literature on consultation-liaison psychiatry. It is evident that the authors were not cognizant of the fact that through the use of a professional librarian, the search logic would have been constructed so as to ensure a greater percentage of retrieval. Therefore, it is not surprising that in their study, Mr. Bareta and associates retrieved only 65% of the journal articles by using MEDLARS. However, it is misleading to assume that their result reflects anything more than a misunderstanding of computerized bibliographic retrieval.

At its most basic, MEDLARS is the computerized version of *Index Medicus*, which uses a controlled vocabulary to produce a list of citations by subject. To retrieve the maximum number of citations, the searcher must be familiar with the Medical Subject Headings (MESH) and understand the indexing methods of the database being searched. The ability of the program to include "free text" words from the title and abstract in a search strategy is helpful to the searcher, but it is truly relevant only in cases where the topic is too new to have its own MESH term or the concept is not well covered by indexing.

All professional librarians know the limitations of computerized searching and are careful to explain to their patrons that the best search will not include books, conference papers, chapters from anthologies, and any articles from journals not indexed. But to imply that a computerized literature review will retrieve little more that half of the relevant articles from core journals is utterly false.

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WILLIAM E. BAXTER, M.A., M.S.
SUSAN R. HEFFNER, M.L.S.
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## Dr. Lyons and Associates Reply

SIR: Our article appears to have stimulated considerable *angst* among medical librarians, as this is the third such letter we have responded to. Mr. Baxter and Ms. Heffner's letter is consistent with earlier letters on two points. First, they contend that if only we had used a medical librarian, our search would have been more successful. In fact, we did use a medical librarian, and she assisted us in developing the search strategy we used. Several passes through the database were made to identify which strategy appeared to be most effective. We do not see the shortcomings of the computerized search as reflecting on the librarian. Furthermore, we would again caution that, increasingly, computerized literature searches are advertised for use by persons who are not librarians. We suspect that searches by untrained individuals would be less thorough than the one we published.

Second, Mr. Baxter and Ms. Heffner claim that our results are "utterly false." We see this accusation as rather reckless, particularly since our results are quite consistent, in terms of identified relevant articles and not-identified irrelevant articles, with other reports on the accuracy of computerized searches (1–4). Rather than accusations and uncorroborated testimonials (5), empirical documentation of accurate methods of searching computerized literature databases is needed.

We have no doubts that computerized literature searches are an important contribution to the advance of science. They provide an important first step toward identifying key articles in a field of inquiry. Our results and the findings of others (1–4), however, caution that these searches are not sufficient to identify all key articles. Such a statement seems neither revolutionary nor heretical. Mr. Baxter and Ms. Heffner should attempt to replicate our study before deciding that our results are false. If nothing else, they should talk to some of their patrons several months after providing them with computerized searches and see just how complete these searches have proved to be.

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JOHN S. LYONS, PH.D.
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JOSEPH BARETA, M.S.
JOSEPH ZORC, B.A.
*Chicago, Ill.*

## Maladaptive Denial of Pregnancy

Sir: David H. Strauss, M.D., and associates have cogently argued for the inclusion in *DSM-IV* of a subtype of adjustment disorder called "with maladaptive denial of physical disorder" (1). Although I agree that such a subtype would have great clinical utility, I am concerned that its proposed wording leaves out a related entity which is important to clinicians: the maladaptive denial of pregnancy. Although pregnancy is not a disorder, denial of pregnancy is a serious psychiatric symptom that may place a woman and her fetus at high risk of complications, such as lack of prenatal care, postpartum emotional disturbance, precipitous or unassisted delivery, fetal abuse, and neonaticide (2, 3).

Inclusion of maladaptive denial of pregnancy in this proposed subtype would facilitate its recognition, characterization, and treatment. This could be accomplished by changing the language to "maladaptive denial of physical condition." The text could also specifically mention that denial of pregnancy is included, in order to underscore this point and avoid confusion. As with other symptoms covered by this subtype, it would be differentiated from psychotic denial of pregnancy occurring in the context of other axis I disorders (4). It could also be distinguished from pregnancies kept secret from others but not actually denied by the patient (5).

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LAURA J. MILLER, M.D.
*Chicago, Ill.*

## Dr. Strauss and Associates Reply

Sir: Dr. Miller suggests that the proposed diagnostic category be broadened to include instances of maladaptive denial of pregnancy, which is better described as a physical condition than a physical disorder. We agree, and feel that in circumstances in which, as a reaction to the symptoms, signs, or diagnosis of pregnancy, a woman persistently denies being pregnant or behaves in such a way as to indicate that she minimizes the significance of being pregnant, this diagnosis may be appropriate.

It seems to us, however, that pregnancy would be the only physical condition appropriately included. The term "condition" is nonspecific and could be applied to a range of normal physical changes accompanying, for example, puberty, menopause, or aging. Although denial of these changes may occur and lead to increased risk for the individual (e.g., an elderly person who undertakes a vigorous exercise regimen without consulting a physician), we think such a concept of maladaptive denial would be considerably broader than that which we intended and would be of less clinical diagnostic value. Therefore, we think that rather than change the name of the disorder, it is preferable to note in the criteria that pregnancy is included. We thank Dr. Miller for her thoughtful comments.

DAVID. H. STRAUSS, M.D.
ROBERT L. SPITZER, M.D.
PHILIP R. MUSKIN, M.D.
*New York, N.Y.*

## Evangelical Christian Psychiatrists

Sir: As an evangelical Christian and a psychiatrist, I commend Marc Galanter, M.D., and associates for their excellent article "Christian Psychiatry: The Impact of Evangelical Belief on Clinical Practice" (1). I would like to state that in addition to the Christian Medical and Dental Society, evangelical Christian psychiatrists (also psychologists and other mental health professionals) belong to the American Scientific Affiliation (Dr. Robert L. Herrmann, Executive Director, P.O. Box 668, Ipswich, MA 01938) and to the Christian Association for Psychological Studies.

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WALTER C. JOHNSON, M.D.
*Hanover, Mass.*

## Third-Party Management of Utilization of Health Services

Sir: Although each is fine in its way, neither the article by Gary L. Tischler, M.D., on utilization management of mental health services (1) nor the complementary editorial by Steven S. Sharfstein, M.D. (2) sufficiently emphasized a major liability of claims management as presently practiced in the United States. I refer to the ousting of treating psychiatrists from their direction of ongoing care when their judgment is overridden by claims managers who "advise" altering the kind or intensity of the treatment with the clear purpose of reducing their employer's costs. In some parts of the country this has become a significant barrier to safe, effective treatment.

One example is claims reviewers who suggest that treating psychiatrists use ECT rather than slower pharmacological methods, in order to reduce the length of hospital stay. Another is reviewers who advise that patients who have responded slowly, though successfully, to past treatment be sent directly to a state hospital rather than be treated in a private hospital, where the bill would be paid by the insurer.

Some carriers are becoming providers of care to coteries of captive subscribers, either in their own facilities or through contractors, with the main goal of reducing costs. Requiring subscribers to obtain treatment at the company store is, of course, the most effective way to reduce competition in the private sector. Obviously, it is hard on the private practitioner. What is more important, recent experiences in APA area IV show that it may be very hard on patients.

At its summer meeting, the area IV council proposed that APA attempt to restrain insurers who are now requiring patients to terminate abruptly their ongoing treatment and transfer to company-approved providers. The council was concerned by reports of patients who had been harmed by this practice. 1) A patient finishing up a successful analysis was told by her insurer that her treatment would be covered only if she were to transfer to a therapist provided by a new contract provider. (I am told that there are no psychiatrists on this provider's roster in Ohio.) She was given only two sessions to accomplish this transition. Lacking the funds to continue uninsured, she quit her treatment, telling her analyst that she felt angry, helpless, and overwhelmed. 2) A patient in Cincinnati, who was told to switch to another provider under similar circumstances, attempted suicide and was left with brain damage. 3) A Toledo patient committed suicide in the same scenario.

A therapeutic alliance is a terrible thing to waste. It is established slowly and, once ruptured, may not be easily renewed, as these tragic cases illustrate. These practices will earn the managed medical care industry a legacy of mistrust that will be difficult to overcome. We should make sure that the public does not find us guilty by association. Psychiatry should distance itself from such schemes and expose how they jeopardize our patients.

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DOUGLAS A. SARGENT, M.D., J.D.
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*Reprints of letters to the Editor are not available.*

## Correction

The source of the "Position Statement on School-Based Health Clinics" (June 1991 issue, p. 820) was incorrectly identified. It originated from the American Psychiatric Association Committee on Psychiatry and Mental Health in the Schools. The committee includes Irving H. Berkovitz, M.D. (chairperson), Colleen E. Sari, M.D., Nancy A. Durant, M.D., Henry J. Gault, M.D., Angela M. Callender, M.D., Ravindra M. Manek, M.D., James P. Comer, M.D. (consultant), Charles R. Keith, M.D. (corresponding member), Elizabeth B. Weller, M.D. (consultant), and Roslyn Seligman, M.D. (consultant).

# 1990–1991 Annual Report of the American Board of Psychiatry and Neurology, Inc.

## COMPOSITION OF THE BOARD

At its business meeting in July 1990, the American Board of Psychiatry and Neurology (ABPN) elected the following officers, who began their terms on Jan. 1, 1991: Dr. William E. Bell, President; Dr. Maurice J. Martin, Vice President; Dr. Stuart A. Schneck, Secretary; Dr. Gary J. Tucker, Treasurer; and Dr. Ludwig Gutmann, Executive Committee Member-at-Large.

Dr. William T. McKinney (psychiatrist, Madison, Wis.), nominated by the American Psychiatric Association (APA), was elected to a 4-year term on the board to succeed Dr. Layton McCurdy, who completed his second 4-year term on Dec. 31, 1990. Dr. Peter Silberfarb, M.D. (psychiatrist, Hanover, N.H.), a member of the American Medical Association, was elected to a 4-year term on the board to succeed Dr. John F. McDermott, Jr., who completed his second 4-year term on Dec. 31, 1990. Dr. James Shore (psychiatrist, Denver, Colo.), nominated by APA, was renominated and reelected to serve a second 4-year term as a director. To succeed Drs. Elliott L. Mancall, N. Paul Rosman, and Jack Whisnant, who completed their second 4-year terms on the board on Dec. 31, 1990, Dr. Burton Sandok (neurologist, Rochester, Minn.) was elected to a 4-year term, Dr. Marvin Fishman (child neurologist, Houston, Tex.) was elected to a 3-year term, and Dr. Michael P. McQuillen (neurologist, Lexington, Ky.) was elected to a 1-year term; all are members of the American Academy of Neurology. The scattered terms in neurology were instituted for this election year to even out the rotations. Dr. Ludwig Gutmann (neurologist, Morgantown, W.Va.), nominated by the American Neurological Association, was renominated and reelected to serve a second 4-year term as a director. The names of the 1991 ABPN directors follow; those serving second 4-year terms are not eligible for reelection.

*From the American Medical Association—psychiatry directors:* Dr. Kenneth Z. Altshuler (first term expires Dec. 31, 1992), Dr. Maurice J. Martin (second term expires Dec. 31, 1991), and Dr. Peter M. Silberfarb (first term expires Dec. 31, 1994).

*From the American Psychiatric Association—psychiatry directors:* Dr. William T. McKinney (first term expires Dec. 31, 1994), Dr. James H. Shore (second term expires Dec. 31, 1994), Dr. Peter E. Tanguay (first term expires Dec. 31, 1993), Dr. Lenore C. Terr (first term expires Dec. 31, 1991), and Dr. Gary J. Tucker (second term expires Dec. 31, 1992).

*From the American Neurological Association—neurology directors:* Dr. William E. Bell (second term expires Dec. 31, 1991), Dr. J. Donald Easton (second term expires Dec. 31, 1992), Dr. Ludwig Gutmann (second term expires Dec. 31, 1994), and Dr. Stuart A. Schneck (second term expires Dec. 31, 1993).

*From the American Academy of Neurology—neurology directors:* Dr. Mark L. Dyken, Jr. (first term expires Dec. 31, 1992), Dr. Marvin A. Fishman (first term expires Dec. 31, 1993), Dr. Michael P. McQuillen, M.D. (first term expires Dec. 31, 1991), and Dr. Burton A. Sandok (first term expires Dec. 31, 1994).

Dr. Stephen C. Scheiber is the Executive Vice President of the ABPN.

## EXAMINATIONS

### *Part I*

At the part I (written) examination on April 2, 1991, 2,422 psychiatrists were examined; 1,406 (58%) passed and 1,016 (42%) failed. A total of 789 neurologists (including child neurologists) were examined; 395 (50%) passed and 394 (50%) failed. Table 1 contains the numbers of candidates in each year from 1986 to 1991. The next part I examination will be held on March 31, 1992. Applications for that examination are due no later than Sept. 1, 1991, and are available from the American Board of Psychiatry and Neurology, Inc., 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015.

### *Geriatric Psychiatry*

At the first geriatric psychiatry (written) examination on April 2, 1991, 661 geriatric psychiatrists were examined; 491 (74%) passed and 170 (26%) failed. The next geriatric psychiatry examination will be held in concert with the part I examination on March 31, 1992. Applications for that examination are due no later than Sept. 1, 1991, and are available from the American Board of Psychiatry and Neurology, Inc., 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015. The ABPN anticipates offering this 3-1/2 hour, multiple-choice written examination on an average of once every other year.

### *Clinical Neurophysiology*

The first examination for certification in Added Qualification in Clinical Neurophysiology will be held in concert with the next part I examination, which will be held on March 31, 1992. Applications for that examination are due no later than Sept. 1, 1991, and are available from the American Board of Psychiatry and Neurology, Inc., 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015. It is anticipated that six national sites will be used to administer a 4-hour, multiple-choice written examination. The ABPN anticipates administering this examination an average of once every 2 years.

### *Part II*

At the 1990 part II (oral) examinations held in Seattle (March 11–13), Minneapolis (June 11–12), and Washington, D.C. (Oct. 28–30), 1,629 psychiatrists, 495 neurologists, and 67 child neurologists were examined. For statistics on these examinations, refer to table 2. The examination sites for 1991 are Los Angeles (Jan. 14–15), New Orleans (April 15–16), and Philadelphia (Oct. 28–29).

The current fees for examination are as follows: part I examination fee=$575, part I reexamination fee=$300, part II examination fee=$500, part II reexamination fee (failure of major or major and minor)=$500, part II reexamination fee (failure of minor)=$300, geriatric psychiatry examination fee=$750, geriatric psychiatry reexamination fee=$500, clinical neurophysiology examination fee=$750, clinical neurophysiology reexamination fee=$500.

**TABLE 1. Candidates for ABPN Part I (Written) Examination, 1986–1991**

| | Number of Candidates | | | | | |
|---|---|---|---|---|---|---|
| Physician Status | 1986 | 1987 | 1988 | 1989 | 1990 | 1991 |
| Met requirements | 2,703 | 2,649 | 2,861 | 3,134 | 3,213 | 3,640 |
| Accepted examination | 2,574 | 2,477 | 2,782 | 3,092 | 3,142 | 3,604 |
| Took examination | 2,301 | 2,255 | 2,471 | 2,725 | 2,831 | 3,211 |

## BOARD DECISIONS AND ITEMS OF INTEREST

1. The American Board of Medical Specialties approved the application of the ABPN for certification for Added Qualification in Clinical Neurophysiology at its September 1990 meeting. The examination is available to individuals who meet the requirements and are certified by the ABPN in neurology, psychiatry, or neurology with special qualification in child neurology. The Committee on Certification for Added Qualification in Clinical Neurophysiology was appointed in July 1990 pending approval by the American Board of Medical Specialties, and it held its first meeting in October 1990. For 1991, the committee's members are Dr. Ludwig Gutmann (ABPN neurology director, Morgantown, W.Va.), chairman, serving a 4-year term; Dr. Jasper Daube (neurologist, Rochester, Minn.), vice chairman, serving a 6-year term; Dr. James Albers (neurologist, Ann Arbor, Mich.), serving a 3-year term; Dr. John Brick (neurologist, Morgantown, W.Va.), serving a 5-year term; Dr. Joan Cracco (neurologist, Brooklyn, N.Y.), serving a 4-year term; Dr. Roger Cracco (neurologist, Brooklyn, N.Y.), serving a 3-year term; Dr. William Erwin (psychiatrist, Durham, N.C.), serving a 2-year term; Dr. Mark Hallett (neurologist, Bethesda, Md.), serving a 4-year term; Dr. William Kennedy (neurologist, Minneapolis, Minn.), serving a 2-year term; Dr. Michael McQuillen(ABPN neurology director, Lexington, Ky.), serving a 2-year term; Dr. Lawrence Phillips (neurologist, Charlottesville, Va.), serving a 5-year term; and Dr. Barbara Westmoreland (neurologist, Rochester, Minn.), serving a 6-year term. Certificates issued will be 10-year, time-limited certificates.

2. The ABPN held a conference during its July 1990 meeting. For psychiatry the focus was on subspecialization in addiction psychiatry, and representatives from APA and the American Academy of Psychiatrists in Alcohol and Addictions attended. During the board meeting following the conference, the ABPN voted to proceed with plans to consider offering an examination for certification in addiction psychiatry. The APA Commission on Subspecialization and the APA Board of Trustees approved the subspecialization request of the American Academy of Psychiatrists in Alcoholism and Addictions, and a letter of intent and application has been sent to the American Board of Medical Specialties. This should he reviewed and approved through the American Board of Medical Specialties no earlier than September 1991, and the earliest time an examination could be administered would be in 1993.

For neurology the focus was on child neurology training issues, and representatives from the Child Neurology Society were invited to participate. During the board meeting following the conference, for candidates applying for certification in neurology with special qualification in child neurology, in lieu of the current requirement of 2 years of approved training in pediatrics the ABPN voted to accept 1 year of approved training in pediatrics plus 1 year of approved training in internal medicine. An acceptable alternative to the 1 year of internal medicine is a full year in which a minimum of 8 months of training must be in internal medicine, the details of which must be documented by the internal medicine training director. The composition of these 8 months cannot include rotations in neurology or emergency medicine.

3. The ABPN determined that it will no longer report separately the scores of U.S. and Canadian medical graduates and those of international medical graduates in the annual report. Scores will be reported by pass/fail and new candidate/reexaminee.

4. The ABPN reaffirmed that its part I written examination has a criterion-referenced approach to standard setting.

**TABLE 2. Performance of Physicians Who Took ABPN Part II (Oral) Examination in 1990**

| | | Passed and Were Certified | | Failed | |
|---|---|---|---|---|---|
| Candidate Group | N | N | % | N | % |
| All specialties | 2,191 | 1,368 | 62 | 823 | 38 |
| New candidates | 1,547 | 1,058 | 68 | 489 | 32 |
| Reexaminees | 644 | 310 | 48 | 334 | 52 |
| Psychiatry | 1,629 | 967 | 59 | 662 | 41 |
| New candidates | 1,129 | 745 | 66 | 384 | 34 |
| Reexaminees | 500 | 222 | 44 | 278 | 56 |
| Neurology | 495 | 357 | 72 | 138 | 28 |
| New candidates | 374 | 283 | 76 | 91 | 24 |
| Reexaminees | 121 | 74 | 61 | 47 | 39 |
| Child neurology | 67 | 44 | 66 | 23 | 34 |
| New candidates | 44 | 30 | 68 | 14 | 32 |
| Reexaminees | 23 | 14 | 61 | 9 | 39 |

5. The history of the first 50 years of the ABPN, edited by Dr. Marc Hollender, has been published.

6. The ABPN determined that candidates be notified in writing and orally of the possibility of having a patient in the part II oral examination who has an infectious disease, as in normal practice, which could include HIV-positive patients. As in the past, candidates must still bring their own equipment to examine patients, such as pins and gloves, and the ABPN will request that each neurology and child neurology examination site provide a receptacle for the pins.

7. The ABPN reaffirmed its policy whereby the recertification examination given by the ABPN will not be offered to any individual who has not been certified by the ABPN.

8. The ABPN reaffirmed its policy whereby all licensing and training requirements must be met before application for examination. The only exception is for residents who complete training after Sept. 1 but before Oct. 1. Such applicants may submit an application by the Sept. 1 deadline only if they contact the ABPN office in writing before July 1 to obtain information regarding special application procedures.

9. The ABPN reaffirmed its policy whereby every applicant must have an *unlimited* license to practice medicine in a state, commonwealth, or territory of the United States or a province of Canada. Every applicant is required to submit copies of current license registrations and expiration dates with the application, in addition to documentation of all training.

10. Documentation for training submitted with part I applications must include exact dates of training. The ABPN will accept only certificates that include precise training in the specialty in which the applicant seeks certification. Certificates that state, for example, "resident in Internal Medicine/Psychiatry" or other dual statements will not be accepted as documentation of psychiatry training by the ABPN.

11. The ABPN determined that the appropriate Residency Review Committees of the Accreditation Council for Graduate Medical Education will be advised if apparent problems within residency training programs are discovered during the normal course of reviewing credentials. The training program will be advised if a report is made to the Residency Review Committee. Training directors have been advised that the ABPN has instituted this process.

12. In conjunction with its summer 1991 policy meeting, the ABPN will be holding a retreat that will focus on recertification. Representatives from some of the boards of the American Board of Medical Specialties that have recertification examinations in place have been invited to attend.

13. At the 1990 APA annual meeting the ABPN offered a workshop that focused on recertification. The ABPN psychiatry directors presented information and responded to questions. In addition, the ABPN Executive Vice President and psychiatry directors have participated in plenary sessions and other workshops of APA and the American Association of Directors of Psychiatric Residency Training in an attempt to clarify information and to publicize current issues of interest. A workshop held at the 1991 APA annual meeting focused on subspecialization.

14. At the fall 1990 meeting of the American Neurological Association and the spring 1991 meeting of the American Academy of Neurology, ABPN neurology directors and the Executive Vice President met with the Association of University Professors of Neurology to discuss current issues of the board and to respond to questions. This meeting proved valuable in outlining the board's current policies and training requirements.

## COMMITTEE ON CERTIFICATION IN CHILD AND ADOLESCENT PSYCHIATRY

At its business meeting in February 1990, the Committee on Certification in Child and Adolescent Psychiatry elected the following officers, who began their terms on Jan. 1, 1991: Dr. Joel P. Zrull, Chair; Dr. Theodore Shapiro, Vice Chair; Dr. Lois T. Flaherty, Secretary-Treasurer.

Dr. Catherine DeAngelis, representative on the committee from the American Board of Pediatrics, resigned in 1990, having been elected a director of the American Board of Pediatrics. The committee elected Dr. Walter R. Anyan, Jr. (New Haven, Conn.) to complete her 6-year term.

Dr. Mark L. Blotcky (Dallas, Tex.) was elected to a 6-year term effective Jan. 1, 1992, to succeed Dr. Joel P. Zrull, who completes his 6-year term on the committee on Dec. 31, 1991.

Members of the Committee on Certification in Child and Adolescent Psychiatry are elected to serve one 6-year term and are not eligible for reelection. The members of the 1991 committee are Dr. Joel P. Zrull (Toledo, Ohio; term expires Dec. 31, 1991), Dr. Theodore Shapiro (New York, N.Y.; term expires Dec. 31, 1993), Dr. Lois T. Flaherty, (Baltimore, Md.; term expires Dec. 31, 1993), Dr. Walter R. Anyan, Jr., representative from the American Board of Pediatrics (New Haven, Conn.; term expires Dec. 31, 1994), Dr. Thomas M. Haizlip (Raleigh, N.C.; term expires Dec. 31, 1995), Dr. Kenneth S. Robson (Hartford, Conn.; term expires Dec. 31, 1994), and Dr. William H. Sack (Portland, Ore.; term expires Dec. 31, 1992).

At its Sept. 7–9, 1990, examination in Denver, the committee examined 284 candidates; 189 (67%) passed, 41 (14%) conditioned, and 54 (19%) failed or failed/must reapply. For additional statistics refer to table 3. The 1991 examination will be held Sept. 20–22, 1991, in Baltimore. The 1992 examination will be held Sept. 11–13, 1992, in Chicago. Applications are due by the May 1 preceding the examination and are available from the American Board of Psychiatry and Neurology, Inc., 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015.

The current fees for examination are as follows: application fee=$250, oral examination fee=$550, oral reexamination fee (condition)=$375, oral reexamination fee (failure)=$550, written examination or reexamination fee=$275.

Applicants are required to submit copies of current license registrations and expiration dates with their applications, in addition to documentation of all training. All licensing and training requirements must be met before application for examination.

Other items of interest and decisions made by the Committee on Certification in Child and Adolescent Psychiatry include the following.

1. The committee continues to arrange examinations in a weekend format. This format has been received positively by an overwhelming majority of candidates, examiners, and host facilities.

2. The committee continues to note difficulties with certificates issued to residents. If child psychiatry training is done during general residency, it must be designated as such.

**TABLE 3. Performance of Physicians Who Took Oral Examinations in Child and Adolescent Psychiatry in 1990**

| Candidate Performance | Number | Percent |
|---|---|---|
| All candidates | 284 | 100 |
| Pass | 189 | 67 |
| Condition | 41 | 14 |
| Fail | 36 | 13 |
| Fail, must reapply | 18 | 6 |
| New candidates | 222 | 78 |
| Pass | 145 | 65[a] |
| Condition | 41 | 19[a] |
| Fail | 36 | 16[a] |
| Reexaminees | 62 | 22 |
| Pass | 44 | 71[b] |
| Fail, must reapply | 18 | 29[b] |

[a] Based on total number of new candidates.
[b] Based on total number of reexaminees.

## COMMITTEE ON CERTIFICATION FOR ADDED QUALIFICATION IN CLINICAL NEUROPHYSIOLOGY

The members of this committee were listed earlier in this report. The first examination will be held March 31, 1992. Completed applications are due the Sept. 1 preceding the examination and are available from the American Board of Psychiatry and Neurology, Inc., 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015.

The current fees for examination are as follows: examination fee=$750, reexamination fee=$500.

1. General requirements are as follows.

a) Candidates must be certified by the ABPN in general psychiatry, general neurology, or neurology with special qualification in child neurology.

b) All licensing and training requirements must be met before application for examination.

c) A formal application on the original form must be completed and filed by the deadline. Photocopies of applications will not be accepted.

d) Applicants must have completed a 1-year fellowship in clinical neurophysiology in a program approved by the Accreditation Council for Graduate Medical Education, beginning no sooner than postgraduate year 5. The emphasis can be in any area of interest, but this must be documented by a letter from the training director describing the training and verifying its successful completion. For the first 5 years admission to examination may also be achieved by completing a 1-year fellowship in a clinical neurophysiology program that is clearly identified as a U.S. or Canadian program. The training can also be achieved by practice time in neurophysiology of 3 years full-time or equivalent (6 years at one-half time, etc.).

e) After the initial 5-year period, applicants will be accepted for examination only if they have successfully completed a 1-year fellowship program in clinical neurophysiology approved by the Accreditation Council for Graduate Medical Education.

2. Certificates will be issued for a 10-year, time-limited period, after which recertification will be necessary to maintain active certification.

3. Examinations will be given once a year or once every other year depending on the number of candidates.

4. For additional information the "Information for Applicants for Certification in Added Qualification in Clinical Neurophysiology" may he obtained from the American Board of Psychiatry and Neurology, Inc., 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015.

# The American Board of Psychiatry and Neurology, Inc.: Report on the 1990 Examinations

*The following successfully completed the Board examination in March 1990.*

## PSYCHIATRY

Sharone Ann Abramowitz, M.D., Oakland, CA
Balkozar Seifeldin Adam, M.D., Little Rock, AR
Richard T. Adamson, M.D., Seattle, WA
Frederick Philip Alpern, M.D., Baltimore, MD
Naleen Naupaka Andrade, M.D., Honolulu, HI
Deanna Louise Armstrong, M.D., Houston, TX
Scott Chester Armstrong, M.D., Washington, DC
Dolph James Arnicar, M.D., Encinitas, CA

Joseph Gordon Babin, M.D., Cheyenne, WY
Patrick Desmond Bacon, M.D., Denver, CO
Anthony G. Bassanelli, M.D., East Amherst, NY
John Battaglia, M.D., Dallas, TX
Dennis Dean Beedle, M.D., West Newton, MA
Daniel Mark Begel, M.D., Milwaukee, WI
Benjamin Bensoul, M.D., San Diego, CA
Alla Berdich, M.D., Northbrook, IL
Judith Leah Berg, M.D., New York, NY
Alan Lee Berkowitz, M.D., Encinitas, CA
Bettina Eloise Bernstein, D.O., Salem, OR
Michael James Bernstein, M.D., Portland, OR
Paul Wesley Best, Jr., M.D., Midland, TX
David Henry Beyer, Jr., M.D., Hillsboro, TX
Bruce Charles Black, M.D., Silver Spring, MD
Robert Vincent Blanche, M.D., Baton Rouge, LA
Paul Bradley Bohn, M.D., Santa Monica, CA
Judith Margarete Bowen, M.D., Topeka, KS
Michael John Brase, M.D., Long Beach, CA
Lawrence Braslow, Jr., M.D., Venice, CA
Robert Crocker Brasted, Jr., M.D., Portland, OR
Anne Louise Buchinski, M.D., Seattle, WA
Gregory Charles Bunt, M.D., Yonkers, NY
Vivien Kleinman Burt, M.D., North Hollywood, CA

John William Cain, M.D., Dallas, TX
Cherye Celeste Callegan, M.D., Dallas, TX
Giovanni Caracci, M.D., New York, NY
Anavel Osorio Carin, M.D., Elmont, NY
Jay Cornel Carlson, M.D., Denver, CO
Mark Joseph A. Cerbone, M.D., FPO Seattle, WA
Richard Alan Charles, D.O., Brooklyn, NY
Chi Ping Margaret Chu, M.D., Elmhurst, NY
Leslie Lucien Citrome, M.D., Spring Valley, NY
Cheryl Ann Clark, M.D., Denver, CO
Robert Carl Clark, M.D., Denver, CO
Robin LaRae Clark, M.D., Elgin, IL
Anthony Lee Claxton, M.D., Forney, TX
Cindy Clover, M.D., Denver, CO
Mari Lois Johnson Cole, M.D., Wichita Falls, TX
Brian Doyle Coleman, M.D., Seattle, WA
David Howard Conney, M.D., New York, NY
John Howard Coverdale, M.D., Houston, TX
Martha Lynn Crowner, M.D., New York, NY

Evelyn Earlene DalPozzo, M.D., Denver, CO
Ernani John D'Angelo, M.D., Huntington Beach, CA
John Rodney Debus, M.D., Dallas, TX
Dorothea L. DeGutis, M.D., Chicago, IL
Melissa Derfler, M.D., Irvine, CA
Dickson Stewart Diamond, M.D., Los Angeles, CA
Steven Franklin Dingle, M.D., Mesa, AZ
Paula C. Dobbs-Wiggins, M.D., Dallas, TX
Dorcas Jean Dobie, M.D., Seattle, WA
Janice Bebe Dorn, M.D., Phoenix, AZ
Stephen Edward Dossick, M.D., San Francisco, CA
Allison Jane Doupe, M.D., South Pasadena, CA
David Adam Downs, Jr., M.D., Omaha, NE

Ronald Gayle Early, Ph.D., M.D., Seattle, WA
Marta Maria Echevarria-Gonzalez, M.D., Mesquite, TX
Ann Thomas Echols, M.D., Phoenix, AZ
John Ray Edwards, M.D., Burlington, VT
Glen Raymond Elliott, M.D., San Francisco, CA
Robert Arthur Evans, M.D., Tucson, AZ

Janet Marie Fairbanks, M.D., Haworth, NJ
Antoinette Marie Falk, M.D., Columbia, MD
Basil Mohamed Farid, M.D., Sugarland, TX
Robert Francis Fearnot, M.D., Killeen, TX
Cheryl Lee Feigal, M.D., Oklahoma City, OK
Richard C. Fettes, M.D., Anchorage, AK
Vicki M. Fiore, M.D., Englewood, NJ
Judith Ann Fisher, D.O., Mexico, MO
Paul Stuart Fishman, M.D., San Francisco, CA
Mary Ann Flatley, M.D., San Antonio, TX
Esther Dennis Fridman, M.D., Teaneck, NJ
Janine Bergerac Fromm, M.D., Berkeley, CA
Linda Jo Fuller, D.O., Alameda, CA

Gloria Ann Gage, D.O., Fort Worth, TX
Ihor Anton Michael Galarnyk, M.D., Palm Springs, CA
Eduardo Garcia-Ferrer, M.D., Manchester, MO
John David Garmon, M.D., San Diego, CA
Joseph Alvin Gartner, M.D., Los Angeles, CA
Gerry Francis Gaviola, M.D., Edison, NJ
Randy Steven Gergel, M.D., St. Louis, MO
Shoshana Gerson, M.D., Los Angeles, CA
Tapobrata Ghosh, M.D., Berkeley, CA
Monika Gierz, M.D., Riverside, CA
Stuart Ballon Gluck, M.D., Los Angeles, CA
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Karl Goodkin, M.D., Miami, FL
Manju R. Goyal, M.D., Mesquite, TX
Cathal Patrick Grant, M.D., Houston, TX
Benjamin Cesare Grasso, M.D., Eagle River, AK
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Judith J. Greenberg, M.D., Huntington, NY
Paul Martin Grekin, M.D., Seattle, WA

James Moffett Hageman, M.D., San Antonio, TX
Deborah Jean Hales, M.D., Palo Alto, CA
Ellen Haller, M.D., San Francisco, CA
Tora Hanssen, M.D., Berkeley, CA
Thomas Gray Hardaway, M.D., Harker Heights, TX
R. Andrew Harper, M.D., Houston, TX
Lynne Louise Haynes, M.D., Palo Alto, CA
Saul Herschel Helfing, M.D., Fresno, CA
Robert Alan Herman, M.D., New York, NY
Abilio Agapito Hernandez, M.D., Montebello, CA
Paul Brently Hicks, M.D., Temple, TX
Debra Ann Hill, M.D., Mission Viejo, CA
Mark Reeves Hoerr, M.D., Seattle, WA
Eve Katherine Hohly, M.D., Hutchinson, KS
Peter John Holland, M.D., Aptos, CA
Cheryl Ann Hollingsworth, M.D., Las Cruces, NM
Robijn Kerst Hornstra, M.D., Kansas City, MO
Josie Ann Hudson, M.D., Laredo, TX

Vijayababu Jampala, M.D., Temple, TX
Stephen Paul Jarvis, M.D., St. Joseph, MO
Ajitkumar Naraindas Jetmalani, M.D., Portland, OR
James Blake Jones, M.D., Seattle, WA
Robert Sheldon Jones, M.D., Vallejo, CA

Marcia Anne Kahn, M.D., Portland, OR
Eric W. Kaplan, M.D., Denver, CO
Jasjit Kaur, M.D., Anaheim, CA
Jennifer Rego Kearney, M.D., North Hollywood, CA
Sidney Arthur Kelt, M.D., Desoto, TX
Christopher Charles Kessler, M.D., Sepulveda, CA
Richard Fox Hammatt Kirk, M.D., Sonoma, CA
David Michael Klebanoff, M.D., Mesa, AZ
Jan Ellen Kohl, M.D., Kew Gardens, NY
Stephen Frank Kowalski, M.D., Topeka, KS
H. Susan Kower, M.D., Leucadia, CA
Mary Lisa Kuhlman, M.D., Burlingame, CA
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Robert Sacks Martin, M.D., Santa Monica, CA
Gary Lee Martz, M.D., Denver, CO
Jeffrey Edwin Max, M.D., West Des Moines, IA
William McAndrew, M.D., San Diego, CA
Robert Edward McCool, M.D., Jackson, MO
Rex Hammond McGehee, M.D., Denver, CO
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James Randy Mervis, M.D., Sepulveda, CA
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Lawrence Novis, M.D., Kensington, CA

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Terry Osback, M.D., San Francisco, CA
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Peggy Jo Pazzaglia, M.D., Chevy Chase, MD
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Jaye-Jo Portanova, M.D., Playa Del Rey, CA

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Ashok Kumar Rajput, M.D., Westbury, NY
Mark David Ramsey, M.D., Montrose, CO
David Franklin Raney, M.D., Littleton, CO
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David James Seitz, M.D., Del Mar, CA
Michael Scott Seller, M.D., Westminster, CO
Kathleen Sue Sheehan, M.D., Dallas, TX
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Stuart Michael Silverman, M.D., Santa Fe, NM
Henry Peter Silvestri, M.D., Denver, CO
Miles Alexander Simmons, M.D., Houston, TX
Gregory Edward Simon, M.D., Seattle, WA
Mary Kristine Simonson, M.D., Vashon, WA
Anna Marie Horner Singdahlsen, M.D., Shreveport, LA
Surjit Singh, M.D., Columbia, MO
Jeffrey Stuart Skolnick, M.D., Seattle, WA
Douglas Lee Smith, M.D., Honolulu, HI
Gregory Warren Smith, M.D., Seattle, WA
Margaret Ann Smith, M.D., Sacramento, CA
S. Christine Smith, M.D., Palo Alto, CA
Susan Patricia Smith, M.D., Beaverton, OR
Eunmee Sohn, M.D., N. Richland Hills, TX
Randall L. Solomon, M.D., Encinitas, CA
Jose Manuel Soto-Perello, M.D., West New York, NJ
Donald Harvey Stanford, M.D., Berkeley, CA
Michael Cooper Stevens, M.D., Warrenton, OR
Victor Louis Stevens, M.D., Honolulu, HI
Paul Stewart, M.D., San Francisco, CA
Susan E. Stice, M.D., Dallas, TX
Anna-Lisa B. Stonehill, M.D., Newport Beach, CA
Dean James Storer, M.D., Washington, DC
Daniel Thomas Suzuki, M.D., Claremont, CA
Leslie Andrew Sziebert, M.D., Yakima, WA
Richard Robert Szuster, M.D., Ewa Beach, HI

Ahmad Khan Tarar, M.D., Nevada, MO
Jonathan Zack Tepper, M.D., Cupertino, CA
Clark Don Terrell, M.D., San Antonio, TX
Margo Lynn Thienemann, M.D., Woodside, CA
Richard I. Torban, M.D., Palm Desert, CA
Arturo A. Torres, M.D., Houston, TX
Michele Kathleen Toth, M.D., Austin, TX
Janet Elaine True, M.D., San Antonio, TX
Peter Keene True, M.D., Portsmouth, VA
Susan Beckwitt Turkel, M.D., Los Angeles, CA
Scott Alan Turpin, M.D., Dallas, TX

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# HALDOL® Decanoate 100

(HALOPERIDOL) INJECTION 100mg/mL

# HALDOL® Decanoate 50

(HALOPERIDOL) INJECTION 50mg/mL

For IM Injection Only

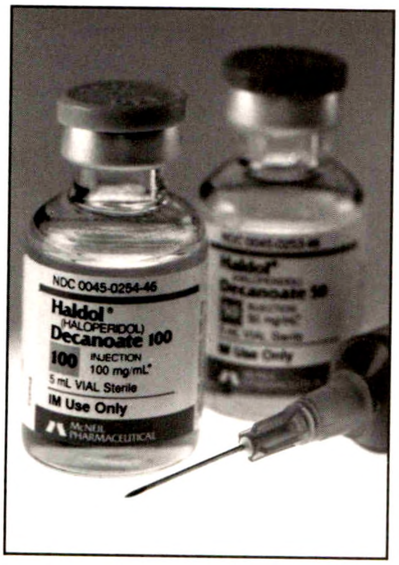
**The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.**

**Contraindications:** Since the pharmacologic and clinical actions of HALDOL Decanoate 50 and HALDOL Decanoate 100 are attributed to HALDOL haloperidol as the active medication, Contraindications, Warnings, and additional information are those of HALDOL, modified to reflect the prolonged action.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

**Warnings:** *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

*Neuroleptic Malignant Syndrome (NMS):* A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.



*Usage in Pregnancy:* (see PRECAUTIONS—Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS—Drug Interactions)

*General:* Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, incuding haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS—Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

**Precautions:** Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used; (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

*Information for Patients:* Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

*Drug Interactions:* Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

*Carcinogenesis, Mutagenesis and Impairment of Fertility:* No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

*Usage in Pregnancy:* Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

*Nursing Mothers:* Infants should not be nursed during drug treatment.

*Pediatric Use:* Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

**Adverse Reactions:** Adverse reactions following the administration of HALDOL Decanoate 50 or HALDOL Decanoate 100 are those of HALDOL haloperidol. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for haloperidol decanoate. As with all injectable medications, local tissue reactions have been reported with haloperidol decanoate.

*CNS Effects: Extrapyramidal Reactions*—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia*—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects*—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

*Body as a Whole:* Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgment, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

**IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate products are administered or prescribed.**

**For information on symptoms and treatment of overdosage, see full prescribing information.**

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

McNeil Pharmaceutical, McNEILAB, INC., Spring House, PA 19477 8/23/89

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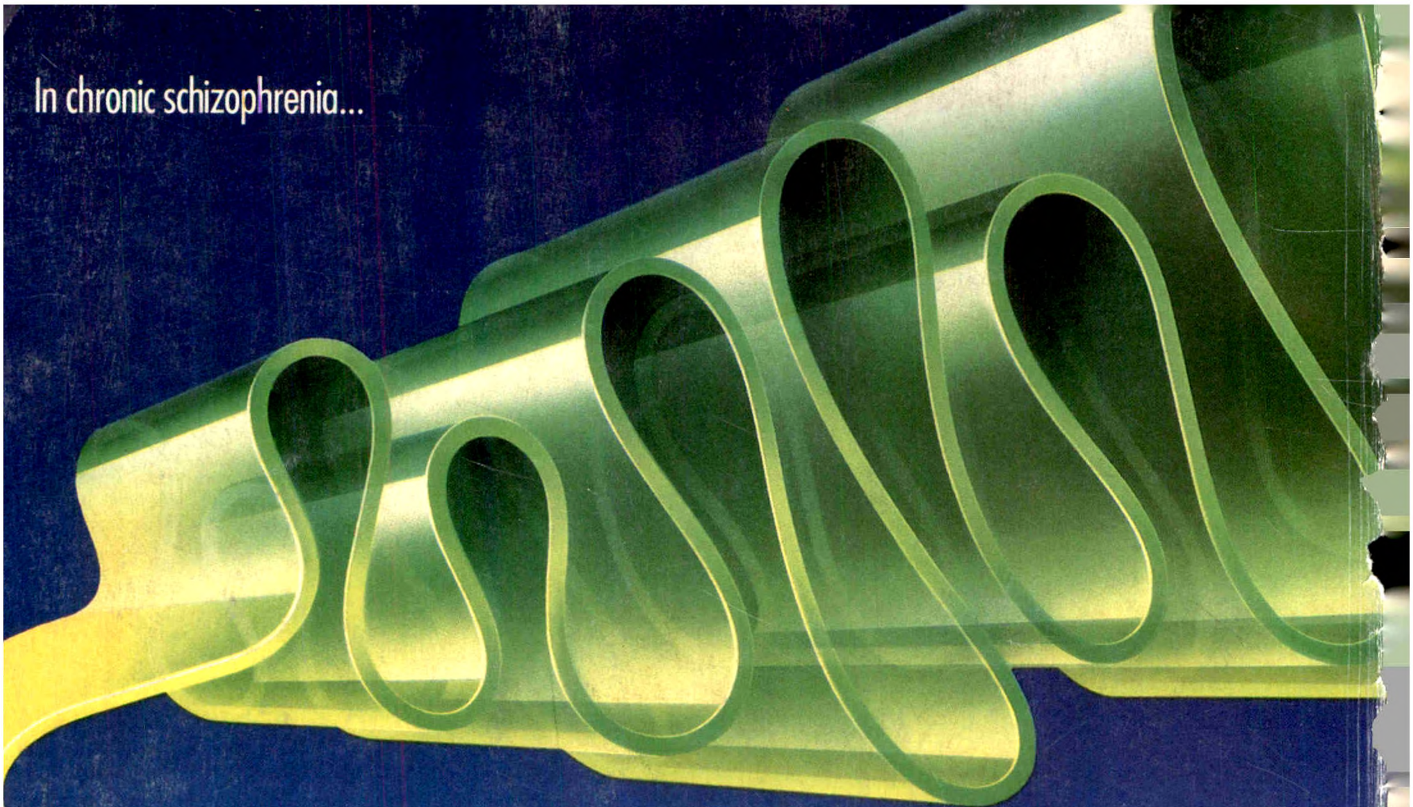
In chronic schizophrenia...



# A successful strategy for reducing relapse

## 74% reduction in relapse rates with haloperidol decanoate[1]

- ▲ Helps reduce the number of hospitalizations
- ▲ Less volume per injection may enhance patient acceptance—an important factor in sustained protection from relapse
- ▲ Convenient, once-a-month dosing
- ▲ Less need for anticholinergics—a proven decrease in the number of patients requiring anticholinergics, over time[1]

During dose adjustment or episodes of exacerbation of psychotic symptoms, therapy with HALDOL Decanoate 100 or HALDOL Decanoate 50 can be supplemented with short-acting forms of HALDOL* (haloperidol). The side effects of the decanoate products are those of HALDOL. The prolonged action of HALDOL Decanoate 100 and HALDOL Decanoate 50 should be considered in the management of side effects.

Please see brief summary of Prescribing Information on adjacent page.

Start depot therapy with

# HALDOL® Decanoate 100

(HALOPERIDOL) INJECTION 100mg/mL

**Reference**

1. Youssef HA. A five-year follow-up study of chronic schizophrenics and other psychotics treated in the community: depot haloperidol decanoate versus other neuroleptics. *Advances in Therapy.* 1989;6(4):186-195.

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